WORLD HEALTH ORGANIZATION
MONOGRAPH SERIES
No. 44

ENDEMIC GOITRE

ENDEMIC GOITRE

CONTRIBUTORS

F. W. CLEMENTS — J. DE MOERLOOSE — M. P. DE SMET
J. C. M. HOLMAN — F. C. KELLY — P. LANGER — S. LISSITZKY
F. W. LOWENSTEIN — W. McCARTNEY — J. MATOVINOVIĆ
S. T. MILCU — J. A. MUÑOZ — C. PEREZ
V. RAMALINGASWAMI — J. ROCHE
N. S. SCRIMSHAW — W. W. SNEDDEN
J. B. STANBURY



WORLD HEALTH ORGANIZATION
PALAIS DES NATIONS
GENEVA

1960

PRINTED IN SWITZERLAND

CONTENTS

PREFACE

Forty years ago, David Marine, one of the pioneers of mass prophylaxis of endemic goitre, claimed that "Simple goitre is the easiest of all known diseases to prevent It may be excluded from the list of human diseases as soon as society determines to make the effort" Society has still not made that effort, although nothing that has since been learned about endemic goitre has cast doubt on the fundamental validity of Marine's assertion Public health authorities in many countries have tended to underestimate the importance of endemic goitre as a threat to physical, social and economic well-being, they have lacked conviction regarding the safety and efficacy of prophylactic measures, and they have been deterred by administrative and technical difficulties

In 1950, the Third World Health Assembly, recognizing the need to stimulate action, recommended that the World Health Organization should undertake a study of endemic goitre and encourage governments to investigate the problem within their territories A study group on endemic goitre was convened in 1952 and its report was published in a special issue of the WHO Bulletin, *which also included a number of original papers dealing with various aspects of goitre control.*

The scope of this first WHO publication on endemic goitre was intentionally limited, its object being to make available a number of reports on studies carried out in various parts of the world and not to offer a comprehensive discussion of the problem of endemic goitre control It was felt, however, that WHO could render a useful service to public health workers, as well as to all those engaged in the study of goitre, by inviting well-known goitre workers to prepare reviews covering all aspects of the subject and collecting these together in a single volume Plans were drawn up for such a monograph, but by the date set for publication, only six chapters had been received and important gaps remained As an interim measure, it was decided to publish these six chapters in a second special issue of the Bulletin *(1958) and to defer publication of the monograph until additional contributions had been obtained This has now been done The present monograph comprises the original six chapters,*

revised and brought up to date by their authors, together with six new chapters covering the history, physiology, pathology and etiology of endemic goitre, experimental studies on goitre, practical aspects of endemic goitre control, and legislation on iodine prophylaxis

Professor W. J Darby of the Division of Nutrition, Vanderbilt University School of Medicine, Nashville, Tennessee, USA, greatly assisted in drawing up the plans for this monograph Valuable technical assistance has been provided by Dr F C. Kelly, Director of the Chilean Iodine Educational Bureau, London, through all stages in the preparation of the material, and helpful suggestions regarding one of the chapters have been received from Professor W. H. Sebrell, Director of the Institute of Nutrition Sciences, Columbia University, New York. To them and to all the contributors who have graciously devoted so much of their time to this undertaking the World Health Organization remains deeply indebted

It is hoped that this monograph will not only serve as a work of reference for all those interested in the control of endemic goitre but will also encourage the adoption of active measures in those countries where endemic goitre is a considerable public health problem but has not yet received the attention it deserves.

HISTORY OF GOITRE

P. LANGER *

Ancient times

In the light of present knowledge of the etiology of endemic goitre, it would not seem unreasonable to infer that this disorder may have been present from time immemorial among the populations of various parts of the world Indeed, it seems extremely probable that the etiological agents known to-day (iodine deficiency, nutritional, hygienic, and climatic factors) exercised the same influence in the distant past as they do now

It is, however, next to impossible to substantiate this presumption with any historical evidence, and consequently we must content ourselves with what references to goitre—often very fragmentary—we can find in the earliest literary sources

One of the oldest references to goitre is attributed to the legendary Chinese emperor Shen-Nung (2838-2698 B C.), who, in his book *Pen-Ts'ao Tsing* (*A treatise on herbs and roots*) is said to mention the seaweed *Sargassum* as an efficacious remedy against goitre [36, 62] However, there are doubts about the very existence of Shen-Nung as an historical personality In the book *Huang Ti Nei Ching*, dating from the period 2697-2597 B C., two types of neck tumour are recognized: those caused by an " accumulation of air " (tumours proper?), and those brought about by an " accumulation of blood " (inflammatory swellings?) [1] Goitre is likewise mentioned in the book *Shan Khai Tsing* (*A treatise on waters and dry lands*), from the period 770-220 B C , which attributes the disease to the poor quality of the water, and further references are to be found in the literary remains of the Han dynasty (206 B C to A.D 220) and the Wei dynasty (200-264 A D.), where, along with drinking-water, deep mental emotions and " certain conditions of life in mountainous regions " are arraigned as causes of goitre. The famous Chinese medical writer Ge-Khun, who lived somewhere between A.D 317 and 419, described a mode of treatment for goitre consisting of *Sargassum* weeds and the weed *Laminaria japonica* Aresch. The

* Endocrinological Institute, Slovak Academy of Sciences, Bratislava, Czechoslovakia

ancient Chinese even used animal thyroid in the treatment of goitre: thus, in the book *Shen Shi-Fan* (420-501 A.D.) mention is made of the use of deer thyroid for this purpose[62] Later *Laminaria religiosa* Aresch was used, references to this seaweed dating back to the 12th century Animal thyroid also continued in use in China, and in the well-known herbal by the eminent Chinese physician Li Shi-Chen (Ming dynasty, 1552-1578) entitled *Pen-Ts'ao Kang-Mu* preparations of pig and deer thyroid are mentioned in the treatment of goitre[62] We may well speculate about how much the Chinese really knew of the function of the thyroid and its relationship to goitre.

References to the treatment of goitre with seaweed and even with animal thyroid, both of which have now been established as containing iodine, lend support to the assumption that the disease in question really was goitre, for it may further be assumed that the recommendation of this therapy by ancient authors was based on the purely empirical observation that it was the most efficacious among a whole series of other modes of treatment then in use. It would indeed be difficult to imagine how seaweed and sponges could for thousands of years have entered as ingredients into preparations of remedies against goitre had no favourable results ensued.

Ancient Hindu accounts of medical literature likewise contain references to goitre Incantations against goitre from the period around 2000 B C. are found in the Atharva-Veda[5] *Galaganda* was the name given by the early Hindu physicians Susruta and Charaka (about 500 B C.) to tumours of the neck These tumours are generally considered to have been goitres,[15, 31, 36] although Greenwald holds a different opinion in spite of the fact that the term *galaganda* is used to this day in India to denote goitre.[21]

Tumours of the neck were also known in ancient Egypt, where, according to the Ebers papyrus (about 1500 B C), they were treated surgically[11] Local applications containing, among other components, salt from Lower Egypt (sea salt?) were used in the treatment of these tumours It would nevertheless be difficult to decide whether endemic goitre was known at that time According to Mettler, the operations reported in the Ebers papyrus include thyroidectomy[51] Wilke, on the other hand, states that no goitres can be identified, either on mummies or on ancient Egyptian paintings.[72] *In this connexion, however, it has to be borne in mind that* not even the basic proportions of the body are correctly shown in these paintings Jantsch[36] notes that, according to Pliny,[61] goitre was widespread in Africa, but this is obviously an error due to an inaccurate interpretation of the original text. Greenwald maintains that goitre was unknown in Africa at that period.[19]

From ancient times in Western Europe we possess a few accounts by Roman authors that agree about the prevalence of endemic goitre in the Alps Thus, the poet Juvenal (1st century A D) asks: "Quis tumidum guttur miratur in Alpibus?" (Who wonders at a swelling of the neck in the Alps?)[38] The architect Vitruvius (1st century B.C.) writes:" Aequiculis

in Italia et in Alpibus nationi Medullorum est genus aquae, quam qui bibunt afficiuntur turgidis gutturibus " (The Acqui in Italy and the Medulli in the Alps have a kind of water, from drinking which they get a swelling of the neck)[71] With a little imagination Ovid's words " Quodque magis mirum, sunt qui non corpora tantum Verum animos etiam valeant mutare liquores " (And what is more wonderful, there are waters that have the power to change not only the body but also the mind) might be interpreted as reflecting the poet's impressions on seeing a cretin[35] Pliny, too, in the 1st century A.D touches upon the subject of goitre: " Guttur homini tantum et suibus intumescit, aquarum quae potantur plerumque vitio " (Swelling of the throat occurs only in men and in swine, caused mostly by the water they drink),[58] and in various places in his writings he lists whole series of remedies against goitre.[59] Ulpianus (2nd century A D) writes " Tumido gutture praecipue laborant Alpium incolae, propter aquarum qualitatem quibus utuntur " (The inhabitants of the Alps suffer from a big neck, caused by the quality of the water they drink)[32] Caesar is credited with having noted the occurrence of a big neck among the Gauls as one of their peculiarities[34, 63]

Works of celebrated physicians of that period often contain descriptions of neck tumours Nevertheless, the thyroid was not yet regarded as a specific organ and was lumped together with the other neck glands. Goitre was confused with other swellings of the neck (tuberculous glands, lymphadenitis, parotitis, etc.), whence the Greek appellation " βρογχοκήλη " (bronchocele) and the very similar expression in Latin " tumor gutturis " or " guttur tumidum ", which prevailed until the 17th, and to some extent even until the 19th, century

In Hippocratic writings (4th century B C.) one finds the expression " γογγρώνη " (gongrona), which Ambroise Paré (1150-1590) interpreted to mean goitre (*De gongrona ou bronchocoele*), and Littré (1840) also translated as goitre.[35] Another Hippocratic expression " χοιρον " (choiron) was taken to stand for goitre and was subsequently employed in this sense, for instance by Paulus Aegina (7th century).[31] " Botium " is yet another term sometimes encountered Thus, Rogerius Salernitanus (12th century) wrote *De cura botii* The word *struma* was first used by Albrecht von Haller (1708-1777) when he remarked that " Strumis longe plerumque thyreoidam glandulam vitiari vulgo notum est " (It is generally known that goitre is mostly an affection of the thyroid gland)[35] These are but a few of the more important expressions to designate goitre encountered in the literature of the past, and many more naturally exist in various languages

In the well-known Hippocratic treatise on *Air, water and places*, drinking-water is regarded as a cause of goitre (choiron)[31] Celsus (25 B C-A D 45) described a tumour (bronchocele) of the neck situated " between the skin and the larynx that is fleshy only, or may contain a sort of honey-like substance, sometimes even containing small bones and hairs

mixed together", and he recommended incision in its treatment.[15] He was probably the first to attempt to make a distinction between the various forms of tumours of the neck Galen (A.D 132-200) also described an operation for goitre, and was even aware of the danger of damaging the recurrent laryngeal nerve To the glands of the neck (and therefore to the thyroid also), he ascribed the role of secreting a fluid into the larynx and the pharynx

These views were accepted as late as the 17th and the 18th centuries (even after the discovery of the thyroid as a specific organ), by such physicians, for example, as Bartholin (1616-1680), Malpighi (1628-1694), and Boerhaave (1668-1738)[9, 36, 66]

We find, however, very little definite information regarding endemic goitre in the medical works referred to above, or in other writings. A plausible explanation for this is advanced by Hirsch, when he remarks that physicians did not formerly gain their experience in localities where goitre may have been widespread, and had in any case little interest in the diseases of populations as a whole

References to goitre operations are scattered through a great many other works Thus Leonidas of Alexandria (2nd century A D), Aetius de Amida (about A D 550)—who was personal physician to the Emperor Justinian I—and after him Paulus de Aegina (A D. 626-690), all knew about surgical treatment They differentiated between cystic and solid goitre, the former being suitable for operation, but not the latter because of the copious bleeding Medical treatment was also used Galen (A D 132-200) and after him Oribasius (A D 325-403) both knew of the favourable effects of burnt sea sponge Aetius de Amida recommended repeated washing of the neck with sea water, or local applications containing sea salt

The Middle Ages

In the Middle Ages Rogerius Salernitanus (*Chirurgia Rogerii*, 1170), of the Salerno school, Gilbertus Anglicus of the Montpellier school (*Compendium medicinae*, 1240), and Bruno di Longoburgo, a professor at Padua (*Chirurgia magna*, 1252), all described surgical operations for goitre[47] Their works show that all of these eminent teachers knew goitre as such and had come into contact with it in the course of their medical practice.

The medical treatment recommended by the ancients for goitre had not been forgotten. Rogerius Salernitanus advised an electuary containing 13 ingredients, among them the ashes of burnt sea sponge[47] The use of sea sponge persisted in the literature up to the 19th century. Gabriele Fallopio (1523-1562) obtained successes even with 4-6 spoonfuls of sea water, taken daily over a prolonged period.[36] In the Middle Ages goitre was treated in the Alps with preparations concocted from the hypocotyledon of Alpine violets growing in a massive knot[70] The resemblance between

certain tumours on plants and goitre was built into a superstitious belief in Northern Bohemia that goitre affected those who ate gall-nuts [7] There are a great many of these popular superstitions and customs and it is not possible to deal with them all here. In Bohemia and Germany, for example, it was held that goitre was the result of strenuous work or of frequent fits of coughing, and that it occurred in women after a particularly difficult labour—whence arose the custom of tying a lace round the neck of a woman in labour [33] A fairly widespread belief in Europe was that goitre is brought on by the effects of the moon. In Ecuador it used to be customary to rub goitres with saliva at the time of the new moon [31]

During the Middle Ages the most advanced thinkers on medical subjects were the Arabs One of their greatest surgeons, Albucasis (10th century) differentiated between congenital and acquired goitre Of these only the latter, in his opinion, was fit for surgery, and then only if it was not too large [15, 36, 45]

Endemic goitre was sporadically mentioned. Guy de Chauliac (born A D. 1300) wrote "Botium aegritudo regionalis et hereditaria apud multos reputatur" (Goitre [botium] is frequently considered to be a local and hereditary disease), and Lafranchi (died A D 1306) considered hard water, especially that found in the Alpine region and in Lombardy, to be the cause of goitre Arnold de Villanova (1235-1312) left a very interesting piece of advice for those suffering from goitre, viz, that they migrate to another region if less than 25 years of age. He also described goitre in the Lucca province Later, Valescus de Tharanta mentioned goitre as occurring in the province of Foix [32, 34] We may also note that Marco Polo, on his travels across Asia in the 13th century, observed goitre in Yarkand

Reports of the existence of goitre on the American continent prior to the arrival of Europeans have recently given rise to controversies. Léon [41] and Lastres [56] take the expression *coto* or *ccotto*, used by the natives before the time of Colombus, as evidence that goitre did exist in parts of South America at that period Greenwald, on the other hand, maintains that goitre did not appear in that region before the 17th or 18th centuries. [18, 24, 27] According to his interpretation the word *coto* originally meant " heap " or " bunch ", and was only later applied to mumps or goitre

The Renaissance and after

Paracelsus (1493-1541) not only described goitre, but also, in his tract *De generatione stultorum*, attributed the disease to a deficiency of minerals in drinking-water

A vivid description of endemic goitre and cretinism appears in the treatise *Praxeos medicae*, by Felix Platter (1536-1614) of Basle " Wherefore," he wrote, " the disease is frequent in certains regions, in the beginning they write of Egypt, and in Valesia Canton Bremis, as indeed I have seen it myself, and in the Carinthia valley called Bintzgerthal many infants are

wont to be afflicted: who besides their innate simple-mindedness, the head is now and then misformed, the tongue immense and tumid, dumb, a struma often at the throat, they show a deformed appearance and seated in solemn stateliness, staring, and a stick resting between their hands, their bodies twisted variously, their eyes wide apart, they show immoderate laughter and wonder at unknown things."[a] The Zurich chronicler Josias Simmler *(1530-1576)* described cretins in the canton of Valais, Switzerland, and another Swiss chronicler, Johannes Stumpf (1500-1558) recorded the incidence of goitre in the Grisons at Trimmis, Untervaz, Zizers and Igis. The Dutch physician Pieter van Foreest (died 1597) noted that there were many cretins in the province of Valtellina,[5, 13] on the Italian side of the Swiss border In 1601 Johannes Jessenius, a Prague physician, mentioned the occurrence of goitre in various regions (in Bohemia?), and added the strange comment that people considered goitre as a form of adornment.[37] In 1736 Gmelin published accounts of goitre occurring in the Lena river basin in Russia[54] In Poland, too, descriptions of goitre attributed to the poor quality of drinking-water appeared in 1757[42] In the 18th century a remarkable description of endemic cretinism was given by the naturalist H de Saussure of Geneva, who had observed the condition on his Alpine travels and attributed it to the elevation above sea level and to the quality of the air. Other noteworthy accounts were given by Malacarne (1778) and Ackermann (1790), who visited cretins in their dwellings and ascribed the disorder to advanced stages of rickets Fodéré (1796) recorded cretinism in Savoy and in the Aosta valley, but rejected rickets as a cause[13] Endemic goitre was known in Derbyshire, England, in the first half of the 18th century under the name of " Derbyshire neck "[18]

The number of written reports on goitre has multiplied enormously, so that it is not possible to mention them all It must, however, be assumed that if physicians and even laymen in the past described goitre or any other tumours of the neck, the swellings must certainly have been strikingly conspicuous, arresting the attention at first sight. Goitres of the first or even the second degree, as usually classified to-day,[b] probably passed unnoticed, even by physicians, whose interest then lay almost exclusively in curative practice. Perhaps even to-day there are some medical men who do not consider as goitres thyroid enlargements that are hardly perceptible to the eye when the neck is not extended, and refuse to admit that these growths are caused by the same etiological factors as cause large goitres and have the same pathophysiological effects, though perhaps in a somewhat modified degree. Overwhelming testimony from all parts of the world shows, however, *that these small goitres are by far the most frequent, and there are* regions where massive goitres are relatively rare But even medium-sized

---

[a] This translation is quoted from Major, R H (1939) *Classic descriptions of disease*, 2nd ed , Springfield, Thomas

[b] See the chapters *Pathological anatomy of endemic goitre* on page 315 and *Technique of endemic goitre surveys* on page 369 of this monograph

goitres, such as occur relatively frequently, may well escape notice in the normal course of everyday life.

In some regions, it is only when the women remove the head scarf that they wear knotted under their chin and undo the collar of their dress that the goitre is exposed and the full extent of the endemic becomes apparent. Even in our own day, such examinations have revealed a striking frequency of goitre in regions hitherto considered free from this disease, and no doubt a similar frequency would have been no less discoverable by these means in the past, especially in temperate and cold climates. Nor can we ignore the efforts, often ingenious, of individuals affected with prominent goitres to hide them from sight, for the deformity attracts notice, brings—and always has brought—mockery upon the unfortunate sufferer, and may at times induce him to shun the company of his fellows. This is especially true of cretins. Cases are known—exceptional, it is true, yet none the less dramatic—of cretins living in stables among farm animals.

These circumstances must be taken into account when interpreting older reports on goitre. Moreover, goitre has never been a killer among diseases, and this too would go to explain why ancient authors devoted less attention to it than to other diseases. It is probable that none of them considered goitre of the first or even the second degree as a disease, especially if it presented no clinical symptoms. Quite the contrary, indeed, such goitres, we believe, were regarded as normal, particularly in women. But there is one most serious obstacle in the way of a correct interpretation of earlier works on goitre, and that is, and no doubt will continue to be, the confusion made between goitre, tuberculous glands, parotitis and other conditions in the neck.

To fill the gaps left by the lack of literary references we might invoke the help of the creative arts, notably painting. It is well known that many eminent painters painted their female models almost exclusively with a swelling of the lower part of the neck that appears to us to be goitre of the first or second degree. A study of goitre in 16th century art was made by Hunziger,[34] and De Josselin de Jong [32] referred to the appearance of goitre in pictures by van Eyck, Lucas van Leyden, Rubens and Riemenschneider. Rolleston likewise detected goitre in paintings by Weyden, Durer, and Rubens.[64] We are of the opinion, however, that only the first steps have so far been taken to evaluate this rich material. There are cases where a study of ancient works of art may reveal unexpected details, as, for instance, the finding of a picture of a cretin in an old psalter.[50] On the other hand, it is often difficult to decide whether the swelling depicted is to be attributed to endemic goitre or toxic adenoma, and opinions differ regarding the correct interpretation.

Original, and in themselves very interesting, views, supported by historical studies on the prevalence of goitre in various parts of the world [18, 28], have recently been expressed by Greenwald, who arrives at the conclusion

that goitre in many countries is only of recent date His studies show that the history of goitre in some lands resembles the pattern seen in infectious diseases He postulates an infectious agent for goitre which, he claims, was present approximately 2000 years ago in the Alps, and only in the Alps, whence it slowly made its way into the rest of Western Europe and other parts of the world (America, Africa, New Zealand, the Philippines, Ceylon, etc), his view being that goitre spread in these regions only after the arrival of Europeans In many countries its first appearance was marked by severe outbreaks, after which it became less active The disease resembles leprosy in that it is not, in ordinary circumstances, readily communicable but generally requires prolonged exposure. According to Greenwald, the older reports on swellings of the neck in various countries for the most part describe tuberculous glands or parotitis, and some of the earlier accounts are not reliable enough for an opinion to be hazarded. He admits the occurrence in isolated cases of enlargement of the thyroid, but such instances are not to be confused with endemic goitre As far as Greenwald's theories are concerned, it is pertinent to observe that not even the best of historical studies will ever provide a solution to these problems, and that the infection theory will have to be corroborated by biological methods

Anatomy and physiology of the thyroid

In following advances in knowledge of the anatomy and physiology of the thyroid through the Renaissance period, we find a whole series of new concepts springing up Probably the first person to describe the thyroid was Andreas Vesalius (1514-1564) It consists, he said, of "two glands (glandulas ad laryngis radicem adnatas) one on each side of the root of the larynx, which are large, fungus-like, flesh-coloured, and covered with numerous vessels The purpose of these glands . . . is to moisten the lumen of the trachea " [51] The first to differentiate the thyroid from the other organs of the neck, however, was Realdus Colombus (1516-1559), who noted that. "Duae aliae glandulae haerent laryngi asperaeque arteriae, quae feminis sunt quam viris crassiores, hinc laryngis pars prominentior in paucis mulieribus conspicuor est, nam ab earum glandularum crassitie occupatur et sub ea habitat " (Two other glands are attached to the larynx and the rough artery [trachea] and these are larger in women than in men, in few women, therefore, is the protruding part of the larynx more conspicuous since it is rounded out by the thickness of these glands and situated beneath them).[56] Eustachius (1520-1574) discovered the isthmus of the thyroid. Casserio (1561-1616) considered the thyroid to be one organ made up of two parts without any excretory duct. Great credit for ascertaining the anatomical site, size, and weight of the thyroid is due to Wharton (1614-1673) whose work *Adenographia sive glandularum totius corporis descriptio* (*Adenography or a description of the glands of the entire body*)

(London, 1656), contains this description of the gland: " ... it contributes much to the rotundity and beauty of the neck, filling up the vacant spaces round the larynx, and making its protuberant parts almost to subside and become smooth, particularly in females, to whom for this reason a larger gland has been assigned, which renders their necks more even and beautiful ".[82] This extract gives the impression that the author was used to seeing goitres of the first degree in women, and considered them as normal.

In spite of the fact that anatomically the thyroid was fairly well differentiated, its function was far from being understood. For the most part its rôle, with the other neck glands, was supposed to be to humidify the walls of the larynx, the pharynx and the trachea. At one time it was even con-considered, by J. Vercelloni, 1711, and Heister, 1717, to be a receptacle for worms.[46]

Schreger (1768-1833) was the first to notice the special blood supply of the thyroid, which he surmised to be a vascular shunt cushioning the brain against a sudden increase in blood flow. Even the anatomist Herbert Luschka (1820-1874) still considered the thyroid to be an elastic cushion protecting the larynx, trachea, blood-vessels and nerves of the neck against direct muscular pressure.[34] Merkel (1857), and prior to him Boerhaave and Martin, had taught the view that the thyroid strengthens the larynx and modulates the voice.[69] Towards the end of the 18th century, however, Albrecht von Haller (1708-1778) had classified the thyroid, the thymus, and the spleen as ductless glands secreting a special fluid into the bloodstream, and De Bordeu (1776) put forward a theory on internal secretion to the effect that every gland, and similarly every organ in the body, produces specific secretions, which enter the bloodstream and bring about the integration of the entire organism.[66] But the real function of the thyroid remained hidden until the last decade of the 19th century.

Beside these scientific views flourished a host of non-scientific theses, fallacies, and popular superstitions and customs. In the Middle Ages goitre had been regarded as being a visitation of God, and it is so seen for instance in some legends of the 5th to the 7th centuries.[32] Later, the belief spread that goitre could be cured by the touch of the monarch. In France, Clovis I is said to have cured the disease in this manner, and Henry IV, according to his personal physician André Dulaurens (1550-1601),[38] caused 1500 goitres to regress by touching the patients and using the formula " Le roi te touche et Dieu te guerit ". Many English sovereigns practised a similar custom, and between 1662 and 1682, Charles II is alleged to have " touched " 9200 sufferers from the " King's Evil " or scrofula, with which goitre was often confused.[2] On 20 March 1710, according to newspaper reports of the time, Queen Anne again revived the ancient custom of curing goitre by the imposition of hands.[53] This healing power was supposed to be shared by every seventh son of a family,[7] and it was also thought to reside in the touch of a corpse's hand, a superstition known even to Pliny.[60]

Towards the end of the 18th and the beginning of the 19th centuries, knowledge about the thyroid made great advances, owing to the efforts of anatomists, physiologists, and clinicians. Studies on endemic cretinism showed that goitre may have been associated with more serious disturbances of this kind, even though the deeper relationships between goitre and cretinism were as yet unknown

Caleb Hillier Parry (1755-1822) was the earliest to describe exophthalmic goitre, which he first observed in 1786 (the account was published three years after his death in *Unpublished medical writings*).[47, 66] In 1835 Robert James Graves (1797-1853) published, in the *London Medical and Surgical Journal* a report of newly observed thyroid affections in women, associated with heart palpitations and, in one case, with exophthalmos

It is claimed that the first man to connect exophthalmos with goitre was the great Persian physician, Sayyid Ismail Al-Jurjani (about the year A D 1136)[66] In 1722 the ophthalmologist Charles Saint-Yves (1667-1736) described 3 cases of exophthalmos accompanied by cardiac pain and slight goitre, but he failed to see any relationship between these symptoms Some authors think that similar cases had been described earlier by Morgagni (1682-1771), Wiseman (1628-1676), and others In 1802 Giuseppe Flajani described two cases of goitre with palpitation of the heart. Carl von Basedow (1799-1854) reported a case of exophthalmic goitre in 1840, and drew attention to three main symptoms. goitre, exophthalmos, and tachycardia, and Charcot in 1863 pointed out a fourth one, tremor In 1886 Moebius set forth the thyrogenous theory of exophthalmic goitre in these words " Graves' disease is an intoxication of the organism resulting from disturbed thyroid activity ". The first metabolic studies in patients with exophthalmic goitre were made by Friedrich Muller in 1893 and two years later Magnus-Levy showed an increased metabolic rate in these patients This brief historical review of the development of knowledge of thyroid hyperfunction shows that our basic concepts are much less than a hundred years old

Knowledge of thyroid hypofunction—myxoedema, a term introduced by W M Ord in 1878—is of even more recent date, in spite of the claim that Wolfgang Hoefer described it as early as 1657.[47] The first clear and correct description of myxoedema was given in 1873 by William Withey Gull (1816-1890) as " A cretinoid state supervening in adult life in women ".[66] Not only the physicians, but some surgeons also recognized the existence of hypothyroidism, foremost among them being Theodor Kocher (1814-1917), J. L. Reverdin (1842-1929), and his cousin A. Reverdin (1849-1908).

Some of the experimental work that preceded these concepts deserves mention A P Cooper in 1836 carried out thyroidectomy in puppies, and later observed the dulling of the faculties it caused. Wilhelm Rapp noted certain thyroprival symptoms but ascribed them to operational trauma. Moritz Schiff (1823-1896) was the first systematically to carry out total

thyroidectomy (in 1856-57) on various animals, the majority of which later perished. In 1884 he repeated these experiments, and found that death could be prevented by intra-abdominal transplants of the gland.[64] These and a host of other experiments showed that the thyroid plays an essential role in the organism Nevertheless, there were some who categorically denied any function to the thyroid (Munk, 1887; Drobnick, 1888; Arthaud and Magon, 1891), and attributed deficiency phenomena to the injury of adjacent organs, especially the nerves.[65] However, the decisive factor in the final appraisal of the significance of the thyroid came from the work of surgeons. In 1883, at a congress of German surgeons in Berlin, Kocher reported the changes following total thyroidectomy, the overall picture of which he termed *cachexia strumipriva* He attributed this condition directly and with absolute certainty to total extirpation of the thyroid, an operation which, from then on, he rejected completely He stressed the close relationship between cachexia and cretinism, and saw in the loss or impairment of thyroid function a cause common to both The differences between the conditions, he felt, lie in the fact that cretinism is congenital and hereditary. In September 1882, before the Geneva Medical Society, J. L Reverdin described his 14 cases of thyroidectomy and, a few months before Kocher, laid stress on the consequences that supervened 2-3 months after the operation He asked whether some unknown function of the thyroid that had been excised did not enter into play, and from then on decided to discontinue the practice of total extirpation He recollected that in one case he had removed one lobe only and the ill effects had failed to appear. In April-May 1883, in the *Revue médicale de la Suisse Romande* he noted that the changes he had found to follow thyroidectomy were identical with the myxoedema of English authors, and termed them " myxœdème opératoire ". The long drawn out polemic between Kocher and Reverdin as to who had priority in these observations was recently summarized (1951) in detail by Bornhauser.[5]

The 19th and 20th centuries

The 19th century witnessed substantial progress in biological and medical research, supported more and more by objective and precise methods The number of reports on endemic goitre grew rapidly and great interest was shown in ascertaining the actual prevalence of goitre and cretinism in various regions. The first of these epidemiological studies was, in all probability, dictated by military needs; this was when Napoleon ordered a systematic investigation of goitre because of the large numbers of young men from certain regions who were rejected by recruiting boards as unfit for military duties He might have been prompted to this step by the vivid impression made on him by the populations stricken by cretinism which he saw at the time of his march into Italy through the Valais [13]

Towards the end of the 18th and the beginning of the 19th centuries, knowledge about the thyroid made great advances, owing to the efforts of anatomists, physiologists, and clinicians. Studies on endemic cretinism showed that goitre may have been associated with more serious disturbances of this kind, even though the deeper relationships between goitre and cretinism were as yet unknown.

Caleb Hillier Parry (1755-1822) was the earliest to describe exophthalmic goitre, which he first observed in 1786 (the account was published three years after his death in *Unpublished medical writings*) [47, 66] In 1835 Robert James Graves (1797-1853) published, in the *London Medical and Surgical Journal* a report of newly observed thyroid affections in women, associated with heart palpitations and, in one case, with exophthalmos

It is claimed that the first man to connect exophthalmos with goitre was the great Persian physician, Sayyid Ismail Al-Jurjani (about the year A D 1136) [66] In 1722 the ophthalmologist Charles Saint-Yves (1667-1736) described 3 cases of exophthalmos accompanied by cardiac pain and slight goitre, but he failed to see any relationship between these symptoms Some authors think that similar cases had been described earlier by Morgagni (1682-1771), Wiseman (1628-1676), and others. In 1802 Giuseppe Flajani described two cases of goitre with palpitation of the heart. Carl von Basedow (1799-1854) reported a case of exophthalmic goitre in 1840, and drew attention to three main symptoms goitre, exophthalmos, and tachycardia, and Charcot in 1863 pointed out a fourth one, tremor. In 1886 Moebius set forth the thyrogenous theory of exophthalmic goitre in these words· " Graves' disease is an intoxication of the organism resulting from disturbed thyroid activity " The first metabolic studies in patients with exophthalmic goitre were made by Friedrich Muller in 1893 and two years later Magnus-Levy showed an increased metabolic rate in these patients. This brief historical review of the development of knowledge of thyroid hyperfunction shows that our basic concepts are much less than a hundred years old

Knowledge of thyroid hypofunction—myxoedema, a term introduced by W. M. Ord in 1878—is of even more recent date, in spite of the claim that Wolfgang Hoefer described it as early as 1657 [47] The first clear and correct description of myxoedema was given in 1873 by William Withey Gull (1816-1890) as " A cretinoid state supervening in adult life in women ". [66] Not only the physicians, but some surgeons also recognized the existence of hypothyroidism, foremost among them being Theodor Kocher (1814-1917), J. L Reverdin (1842-1929), and his cousin A. Reverdin (1849-1908)

Some of the experimental work that preceded these concepts deserves mention A P Cooper in 1836 carried out thyroidectomy in puppies, and later observed the dulling of the faculties it caused Wilhelm Rapp noted certain thyroprival symptoms but ascribed them to operational trauma. Moritz Schiff (1823-1896) was the first systematically to carry out total

this theory was Boussingault who, in 1831, drew attention to the significance of a limestone soil in the Cordilleras of New Grenada (now Colombia).[8] Further studies [14, 46] suggested that the goitrogenic action of the limestone was due more to the magnesium than to the calcium salts The part played by minerals in the production of goitre is still unsettled, but experimental work by Hellwig [30] and others has shown that, under certain conditions, calcium can exert a goitrogenic action

A relationship between iodine and goitre seems to have been suspected soon after Courtois isolated this element in 1811 from ashes of the seaweed *Fucus vesiculosus* [16] By 1816, iodine had already been used in the treatment of goitre by Proust,[44] and in 1820 Coindet (1774-1848) independently recommended iodine preparations for this purpose He was prompted to make this suggestion through his discovery that *Fucus vesiculosus* had been used by Richard Russell (1700-1771) in England for the treatment of goitre and that in 1819 iodine had also been found by Andrew Fyfe (1795-1891) in sea sponges, long famed as a goitre remedy He suspected that iodine was the active substance in both cases On 25 July 1820, he gave a lecture to the Swiss Society of Natural Sciences in Geneva, in which he described the pathological anatomy of goitre, stressed that the thyroid was an organ *sui generis*, albeit of unknown function, and reported the first results of iodine therapy [6] Soon, however, the use of iodine in the treatment of goitre met with marked opposition because of its toxic side-effects (cachexia, cardiac upsets, disturbed menses, subacute and even chronic intoxication) Coindet laid emphasis on correct dosage, for he himself noticed no untoward effects in his 150 patients, whom he kept on low doses He interrupted medication at the very first sign of intoxication, and later adopted an intermittent form of therapy Jean-Louis Prevost (1790-1850), however, found that with Coindet's regime certain ill effects still appeared, in spite of every care, and he conceived the idea of a steady reduction in dosage At the same time, he observed that amounts as low as 0 9-2 0 mg produced a noticeable effect on goitre, from which he deduced that goitre might be caused by a deficiency of iodine or bromine in water and that prophylactic doses of these elements might help prevent its onset. In 1846, together with the Italian, A C Maffoni, he put forward for the first time the theory that endemic goitre is due to iodine deficiency [63]

The iodization of salt as a method of preventing goitre was first suggested by Boussingault in 1833 (as described by Kelly & Snedden on page 43 in their chapter on the *Prevalence and geographical distribution of endemic goitre*) In 1849, Grange, in a letter addressed to the French Academy of Sciences, recommended the iodization of kitchen salt in the ratio 1 10 000 [17] During the next two years, the French chemist Chatin published a series of papers describing the results of systematic iodine determinations on air, water, soils, and animal and vegetable foods from various localities in France On the basis of his findings, he was able to divide these localities into

In 1845, a special commission was appointed by King Carlo Alberto of Sardinia to study the extent of goitre throughout his Kingdom (the provinces of Savoy, Nice, Piedmont, Genoa and the island of Sardinia) and recommend means of combating it[68] A similar commission was set up in 1864 by the French Government Ten years later this commission submitted its report, in which it was recorded that 370 403 persons in France above the age of 20 had goitre, and that in addition there were approximately 120 000 cretins and idiots (the total population of France at that time was around 36 million) At this period, government departments in several countries began to show interest in the prevalence of goitre and cretinism Statistical reports, based chiefly on conscription records, appeared In 1881, for example, Sormani published the results of the examination of over 2 million recruits carried out between 1863 and 1876, out of whom 42 863, i e, 2 09 % had been declared unfit because of goitre.[32] Thus, the widespread character of endemic goitre became evident Nevertheless, all the writings from this period are characterized by the lack of a uniform criterion for the evaluation of goitre (this still holds true today in spite of the great progress that has been achieved) Differences between the findings of various observers were considerable, and it was practically impossible to make comparative studies without running the risk of reaching paradoxical conclusions Moreover, most of the studies, being based on military statistics, included only males, who are much less affected by goitre than females

During the last 50 years, hundreds of epidemiological studies on endemic goitre have been carried out in all parts of the world, and attempts have been made to correlate prevalence with geophysical and geochemical features, as well as with various other environmental factors These studies are reviewed country by country by Kelly and Snedden in the chapter *Prevalence and geographical distribution of endemic goitre* (pages 27-233), and no attempt will be made to summarize them here

Realization of the world-wide character of endemic goitre and of its public health importance focused attention on its etiology and on methods of mass prophylaxis As early as 1867, Saint-Lager[67] had listed 43 different views on the causes of goitre, expressed by 378 authors. Nineteen of these views attribute the disease to various properties of water, to its origin, or to deficiency or excess of certain minerals, 11 to properties of the atmosphere (humidity, temperature, chemical composition, lack of sunshine or electricity, etc), 6 to faulty nutrition, poverty and insanitary living conditions; and the remaining 7 to sundry other causes, such as alcoholism and consanguinity in marriage.

The view that goitre is caused by drinking certain kinds of water had been widely held since ancient times, as has already been mentioned It was generally thought that a high content of certain minerals, particularly calcium salts, was the factor principally involved. A strong advocate of

Present-day practice in the prophylaxis of goitre is based on the teachings of David Marine, who in 1915 declared that " endemic goitre is the easiest known disease to prevent ". In the same year, Hunziger proposed that goitre prophylaxis with iodized salt be carried out in Switzerland.

The first large-scale trials with iodine were carried out in 1916-1920 by Marine and Kimball in Akron, Ohio, USA, when they gave to about 5000 schoolgirls, aged between 11 and 18, a daily dose of 0 2 g of sodium iodide in water for 10 days each spring and autumn (4 g of sodium iodide per year).[41, 48, 49] The results of these trials demonstrated conclusively the prophylactic value of iodine and the absence of side-effects, despite the relatively high doses. Mass prophylaxis with iodized salt was first attempted in Michigan in 1924 In five years, the goitre rate fell from 38 6% to 9%; no toxic effects at all were observed Nevertheless, the fear of Jod-Basedow and other side-effects has lingered on and continued to hamper the introduction of iodized salt on a community scale in other areas Thus, the US Department of Agriculture Bureau of Chemistry insisted on every container of iodized salt being marked with a skull and cross-bones because iodine was considered to be a poison It was also feared by some surgeons that the use of iodized salt would bring an epidemic of exophthalmic goitre in its train. Many families refused, on various grounds, to use iodized salt, and an attempt to enforce its use by federal legislation failed.

In spite of these difficulties, the consumption of iodized salt gradually increased in the USA, and during the 1920's the iodization of salt began to be practised also in Switzerland and in the Valtellina province of Italy; Canada, the Netherlands, New Zealand, Poland and certain parts of Germany followed a little later, and, more recently, iodized salt has also come into use in some states of Central and South America

Further details of the early trials with iodized salt and of the administrative and legal problems encountered will be found in Kimball [41] and in the chapters specifically devoted to these questions in this monograph (see pages 386, 404, 411 and 443)

In concluding this historical survey—which makes no claim to being a comprehensive study of the subject—it should be pointed out that to date no serious objection has been raised against iodine prophylaxis although the universal and absolute validity of the iodine-deficiency theory has often been questioned Today, we possess an abundance of reports from all parts of the world on the favourable effects of iodine prophylaxis, and if this method were universally adopted, it would appear possible at least to achieve a great reduction in endemic goitre in the world, if not to eradicate it completely This requires, however, concentration of effort and a long-term, co-ordinated follow-up of the effects of prophylactic treatment

four zones, in which the incidence of goitre was inversely proportional to the iodine content of the environment As a protection against goitre, he recommended the supply of foodstuffs from non-goitrous regions, the drinking of wine and pure, running water, the consumption of good food of animal origin, and finally the use of iodized salt. Chatin's work was repeated several times, but with varying results This is not surprising in view of the extraordinary difficulties involved in the micro-determination of the iodine content of natural substances Some investigators (e.g., Nadler, 1861) considered Chatin's results to be faulty because they themselves failed to detect iodine in the atmosphere, in water, or in foodstuffs.[14] A tribunal appointed by the French Academy of Sciences reported unfavourably and Chatin's findings fell into oblivion

Thus far, there had been no real experimental evidence to connect iodine with thyroid metabolism, but, in 1895, Baumann demonstrated that the thyroid contains a surprisingly large amount of iodine and succeeded in isolating from the thyroid a substance which he called " thyroiodine ", containing 10% of iodine. When used in physiological experiments, this substance brought about the same effect as thyroid itself.[3] Oswald pursued the study of the chemical composition of the active substances of the thyroid and isolated thyroglobulin in 1899, and Kendall in 1919 isolated crystalline thyroxine,[39] which C R Harington later (1926) prepared in synthetic form [29] These studies were decisive in showing iodine to be *an essential component of thyroid hormone and paved the way for a renewed* interest in iodine therapy and prophylaxis.

The more recent work on the etiology, pathological anatomy and physiology of endemic goitre is discussed elsewhere in this monograph and will not, therefore, be considered here Attention is particularly directed, however, to the pioneer studies of McCarrison in India on the goitrogenic action of polluted water (see pages 157 and 364) and to those of Astwood, Clements, Greer and others on goitrogens in the diet, especially in vegetables of the *Brassica* genus (see pages 66, 194, 281 and 359) A review of the history of cretinism and a discussion of its relationship to endemic goitre will be found in the chapter by Clements (page 245)

Mass prophylaxis of endemic goitre

Increased knowledge of the geographical distribution of endemic goitre and of its frequency and intensity in various regions, together with a deeper understanding of thyroid function and the causation of some of its disorders, has led to a full realization of the social significance of goitre and of its impact on the health of the community. Although the recommendations made in the last century by Boussingault, Grange, Chatin and others for preventing goitre by the use of iodized salt were largely ignored, the concept of mass prophylaxis by administering minute doses of iodine has steadily gained acceptance during the last forty years

43 Lastres, J. B (1958) *Arch ib-amer Hist Med*, 10, 217
44 Léon, L A (1959) *Gac méd (Guayaquil)*, 14, 8
45 Lick, E. (1929) *Das Kropfrätsel*, München
46 McClelland, J (1835) *Trans med phys Soc Calcutta*, 7, 145
47 Major, R H (1954) *A history of medicine*, Springfield
48 Marine, D & Kimball, O P (1920) *Arch intern Med*, 25, 661
49 Marine, D & Kimball, O P (1921) *J Amer med Ass*, 77, 1068
50 Merke, F (1958) *Schweiz med Wschr*, 88, 625
51 Mettler, C C (1947) *History of medicine*, Toronto
52 Müller, H (1949) *Hygiene*, München
53 Neustätter (1928) *Die Medizinische Welt*, p. 199
54 Nikolayev, O V (1955) *Endemicheski zob*, Moskva
55 Ovid, *Metamorphoses*, lib XV, 317-318
56 Pancbaker, G (1925) *Med life*, 32, 97
57 Podach, E F (1951) *Schweiz med Wschr*, 81, 19
58 Pliny the Elder, *Historia naturalis*, lib XI, 37, 68
59 Pliny the Elder, *Historia naturalis*, lib XXV, 109, 2, lib XVI, 32, lib XXVII, 44, lib XXVIII, 51, lib XXX, 12, 3, lib XXXII, 28
60 Pliny the Elder, *Historia naturalis*, lib XXVIII, 9, 1
61 Pliny the Elder, *Historia naturalis*, lib XXXII, 4, 14
62 Popovitsh, P P (1959) *Probl Endokr Gormonoter*, 5, 105
63 Prévost, J-L & Maffoni, A C (1846) *Atti Accad Sci med Torino*, 2, 453
64 Prout, W (1834) *Chemistry, meteorology and function of digestion*, London, p 113
65 Robinson, V (1925) *Med life*, 32, 67
66 Rolleston, H D (1936) *The endocrine glands in health and disease, with a historical review*, London
67 Saint-Lager, J (1867) *Etudes sur les causes du crétinisme et du goître endemique*, Paris, Baillière
68 Sardinia, Commissione nominata d'ordine di S M il re di Sardegna per studiare il cretinismo (1848) *Relazione della commissione* , Torino
69 Skála, J (1911) *Žlaza štítná*, Praha
70 Usteri, A (1926) *Gäa-Sophia* 1, 164
71 Vitruvius, P M, *De Architectura*, lib VIII, 3, 20
72 Wilke, G (1936) *Die Heilkunde in der europäischen Vorzeit*, Leipzig

REFERENCES

1 Backing, Liang (1933) *Arch Gesch Med* 26, 121
2 Bailey, H & Bishop, W J (1944) *Notable names in medicine and surgery*, London, Lewis, p 43
3 Baumann, E (1895) *Hoppe-Seyl Z physiol Chem* 21, 319
4 Bircher, H (1883) *Der endemische Kropf*, Basel
5 Bornhauser, S (1951) *Zur Geschichte der Schilddruse und Kropfforschung im 19 Jahrhundert*, Aarau
6 Boussingault, J B (1831) *Ann Chim Phys*, 48, 41
7 Čižmář, J (1946) *Lidové lekařství v Československu*, Brno
8 Coindet, J F (1820) *Bibl universelle Sci Arts (Genève)*, 14, 190
9 Courcy, J L de, Courcy, C B, de (1949) *Pathology and surgery of thyroid disease*, Springfield
10 Courtois, M B (1813) *Ann Chim (Paris)*, 88, 304
11 Deines, H, Grapow, H & Westendorf, W (1958) *Grundriss der Medizin der alten Agypter*, Bd IV, 1 Teil, Berlin, p 223
12 De Josselin de Jong, R (1928) *Über den Kropf in den Niederlanden* In *Comptes rendus de la Conference internationale du goitre, Berne, 24-26 aout 1927*, Berne, p 119
13 De Quervain, F & Wegelin, C (1936) *Der endemische Kretinismus*, Berlin & Wien
14 Fellenberg, T von (1926) *Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods*, Munchen
15 Foote, M N (1954) *J clin Endocr*, 14, 1385
16 Grange, J (1848) *C R Acad Sci (Paris)*, 27, 358
17 Grange, J (1849) *C R Acad Sci (Paris)*, 29, 695
18 Greenwald, I (1945) *Bull Hist Med*, 17, 229
19 Greenwald, I (1949) *Bull Hist Med*, 23, 155
20, Greenwald, I (1949) *Fed Proc*, 8, 384
21 Greenwald, I (1950) *J clin Endocr*, 10, 1309
22 Greenwald, I (1952) *Bull Hist Med*, 26, 263
23 Greenwald, I (1953) *Ceylon med J*, 2, 140
24 Greenwald, I (1954) *Atti del XIV Congresso Internazionale di Storia della Medicina*, 2, 3
25 Greenwald, I (1955) *J Hist Med*, 10, 227
26 Greenwald, I (1957) *J Hist Med*, 12, 72
27 Greenwald, I (1957) *Tex Rep Biol Med*, 15, 874
28 Greenwald, I (1958) *Bull Hist Med*, 32, 121
29 Harington, C R (1926) *Biochem J*, 20, 300
30 Hellwig, C A (1940) *Arch Surg (Chicago)*, 40, 98
31 Hernandéz, H H (1957) *Rev Soc venez Hist Med*, 5, 149
32 Hirsch, A (1883) *Handbuch der historisch-geographischen Pathologie*, Bd II, Stuttgart
33 Hohn, H (1916) *Schweiz Arch Volksk*, 20, 184
34 Hunziger, H (1935) *Schweiz med Wschr.*, 65, 13
35 Iff, W (1938) *Janus*, 42, 69
36 Jantsch, M (1948) *Der Kropf und seine Behandlung Eine geschichtliche Übersicht*, Wien
37 Jessenius, J (1601) *Institutiones chirurgicae*, Wittenberg
38 Juvenal, *Satire XIII*
39 Kendall, E C (1919) *J biol Chem*, 39, 125
40 Kimball, O P. (1937) *J Amer med Ass*, 108, 860
41 Kimball, O P (1953) *Bull Wld Hlth Org*, 9, 241
42 Kolago, C (1952) *Geomedyczne zagadnienie wola*, Warszawa

PREVALENCE AND GEOGRAPHICAL DISTRIBUTION OF ENDEMIC GOITRE

F. C. KELLY, B.Sc., Ph.D., F.R.I.C.* &
W. W. SNEDDEN, M.A., B.Sc., Ph.D.*

Goitre, as this survey shows in detail, occurs with varying intensity in almost every country, few countries appear to be entirely free from it. The disease has been observed in the far north, in the tropics, and in the far south; it occurs quite independently of climate, season or weather. Moreover, in its incidence goitre makes no distinction of race, nationality, colour, creed or class; the North American, the European, the Chinese, the Himalayan Indian, the Turkoman, and the peoples of Central and South America all suffer from it under certain conditions—some severely, some moderately, some but mildly.

Without doubt the most notorious goitre centres of the world are located in high mountain regions—in Alpine valleys, in the Pyrenees, on the slopes of the Himalayas, and along the Cordillera of the Andes. But goitre is also known to occur with considerable intensity in comparatively low-lying areas and even at sea level; for example, it is seen around the Great Lakes basin between Canada and the USA, in the plains of Lombardy, in the ice-excoriated parts of Finland, and in the low-lying Netherlands. Seven relief maps[a] showing the distribution of endemic goitre in different areas of the world will be found in the appropriate sections of the text (Fig. 1-7). These maps indicate only where goitre has been found but not the severity of the endemic.

Students of iodine geochemistry have a ready explanation for these diverse phenomena. They say that the types of terrain in which goitre is for the most part found, be they at high altitude or low, are just those which have been subjected either to flooding or to intense glaciation and from which most of the soil iodine has been washed out and carried through the rivers to the sea. During the last Ice Age, earlier soils were swept away

* Chilean Iodine Educational Bureau, London, England

[a] These maps have been kindly prepared by Mr C. Dutton, Nitrate Corporation of Chile Limited

In India, there are said to be about 9 000 000 goitre sufferers; and in the USA, the number of men rejected for military service on account of goitre was no less in the Second World War than in the First—namely, five in every thousand examined. It is said [59] that 1 000 000 working men in the USA have hypothyroidism unbeknown to them or their physicians

These and other similar facts are marshalled country by country in the following pages. The survey is divided into two parts, the first covering the Americas and Europe, and the second, Africa, Asia and Oceania.

THE AMERICAS

North America

Canada, United States of America, Mexico

Central America

Guatemala; Honduras, El Salvador; Nicaragua; Costa Rica, Panama, Cuba, Dominican Republic

South America

Colombia; Venezuela; Ecuador; Peru; Bolivia, Chile, Argentina, Paraguay, Uruguay, Brazil

EUROPE

Northern Europe

Iceland, Finland, Sweden, Norway, Denmark, Estonian SSR, Latvian SSR and Lithuanian SSR, Netherlands

Eastern Europe

Poland, USSR (excluding Estonian SSR, Latvian SSR and Lithuanian SSR), Romania, Bulgaria, Yugoslavia, Albania, Greece

Central and southern Europe

Austria, Hungary, Czechoslovakia, Germany, Switzerland, Italy, Sicily and Sardinia, Malta, Spain, Portugal

Western Europe

Belgium, England and Wales, Scotland, Northern Ireland, Ireland, France

AFRICA

North-west and West Africa

Algeria, Morocco; Madeira and Canary Islands, French West Africa, Gambia, Sierra Leone, Liberia, Ghana, Nigeria, British Cameroons, Cameroun, French Equatorial Africa, Angola

North-east and East Africa

Egypt, Sudan; Ethiopia and Eritrea, British Somaliland, Uganda, Tanganyika

Central and South Africa

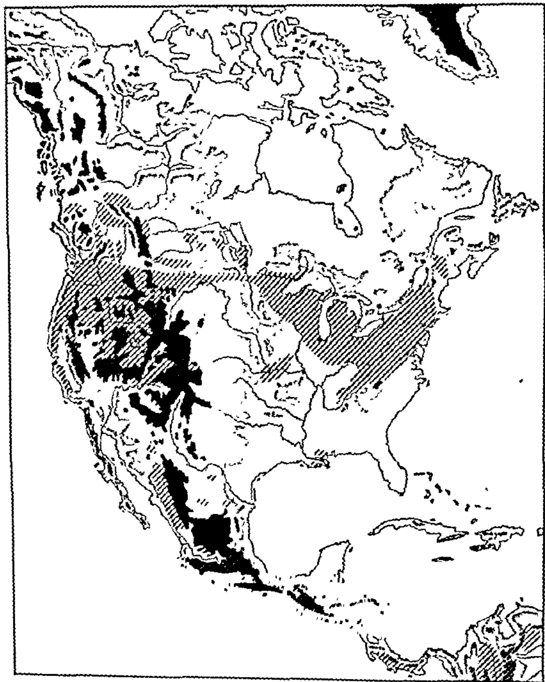
Belgian Congo and Ruanda-Urundi, the Rhodesias, Union of South Africa, Caprivi Strip, South-West Africa; Bechuanaland, Swaziland, Basutoland, Seychelles and Madagascar

and new soil-making materials were generated by the grinding-up of virgin crystalline rock containing, at the most, one-tenth the average iodine content of mature agricultural soils As the ice cover receded, replenishment of the iodine in glacial and postglacial soil materials began—a process which is still in progress The time since the start of this replenishment, that is, the time since the disappearance of the great inland ice-sheets, is *estimated to be 10 000 to 20 000* years *for the central and* northern parts of Scandinavia and the northernmost part of North America, and correspondingly longer for the southern parts of the glaciated areas of Europe and North America This accords with the fact that the frequency distribution of goitre in North America and in a number of countries in Europe, Asia and Australasia shows a close correlation with the areas and extent of quaternary glaciation where soils have not yet been sufficiently saturated with postglacial air-borne oceanic iodine (see *Geochemistry of Iodine* [312])

The number of goitrous people in the world is not known, but if the *statistics available for some countries may be taken as a guide, the total is* probably not far short of 200 million. Although the geographical distribution of goitre has not apparently altered in the last hundred years, the intensity of the disease has substantially declined in certain countries—particularly those which have enjoyed rising standards of living and an enlightened outlook on public health The endemics in Switzerland, the USA and New Zealand, for example, have been largely eliminated within the past thirty-five years through the prophylactic use of iodized salt

Nevertheless, there are many countries where the prevalence of goitre is still exceedingly high and a matter of serious public concern, and many others where the people live so near the critical level of iodine intake that whenever the slender resources of the thyroid gland are abnormally taxed, as, for example, during the nutritional privations of war, epidemic outbreaks of goitre result. Statistics for the year 1952 show that in eight states of Mexico there were over 2 million goitrous people out of a total population of about 10 million, in El Salvador, 329 000 people out of 1 856 000 are affected, Pinotti [230] estimates that there are 11 500 000 cases of goitre in Brazil; in Finland, 2000 operative cases annually out of a population of 3 5 million account for 30 000 days of hospital attendance; in Sweden there are said to be 300 000 people with goitre in a total population of 7 million, Matovinović [480] estimates that some 1 400 000 persons suffer from the disease in Yugoslavia; Hungary has a goitre population of 500 000; [520] and in Italy, Cerletti [703] reckons that no less than 5 million persons are affected, that is, rather more than 10% of the total population. In England and Wales, in 1944, there were estimated to be some 500 000 cases of thyroid enlargement in schoolchildren and young adults, [868] and Taylor [883] has pointed out that the loss sustained by England, Wales and Scotland through failure to iodize salt must be immense if calculated in terms of demands made on the medical services and loss of working time

FIG. 1. NORTH AND CENTRAL AMERICA



The red hatching indicates the areas where endemic goitre has been found

ASIA

Eastern Mediterranean

Turkey, Lebanon, Israel, Iran

Central Asia

Afghanistan, Pakistan, Kashmir, Nepal, Tibet, India; Assam, Ceylon

Far East

Burma, Thailand, Indo-China (Cambodia, Laos and Viet Nam), Malaya, Indonesia; Sarawak, North Borneo, China, Korea, Taiwan, Japan, Philippine Islands

OCEANIA

Australasia

New Guinea, Australia and Tasmania, New Zealand

Pacific Ocean

Fiji Islands, Tonga (Friendly Islands), Cook Islands, Hawaiian Islands

The occurrence of endemic goitre has been recorded in all the above countries So far as can be ascertained there is no published information relating to countries not named above

Among those who have previously dealt comprehensively with the geographical distribution and prevalence of endemic goitre on a continental or world scale are Hirsch,[8] Saint-Lager,[12] Bircher,[1] Clemow,[4] McCarrison,[9] Eggenberger,[6] De Quervain & Wegelin,[5] Pfluger,[11] McClendon,[10] Greenwald,[7] the Chilean Iodine Educational Bureau, London,[3] and the Oficina Educacional del Yodo, Santiago, Chile.[2]

PART I—THE AMERICAS AND EUROPE

North America

Canada

Proceeding through Canada from west to east, centres of goitre are first encountered in British Columbia Some 50 or 60 miles[a] from Vancouver, going inland from the head of Howe Sound, the disease is found in the Pemberton valley and in the area watered by the Lillooet and Birkenhead rivers. An interesting account of this district has been given by Keith,[22] who relates that fifty years ago European settlers in Pemberton Meadows suffered so severely from goitre, both in themselves and among their cattle, pigs and horses, that they almost decided to leave the valley. Writing in 1949, MacDermot[23] records that owing to the administration of supplementary iodine in food and drinking-water, Pemberton Meadows is now a healthy and thriving community

[a] 1 mile = 1 6 km

Stonewall, both in the Winnipeg area, 85% of the children were sufferers The Indian School at Waugh, in the extreme east of the province, was free from goitre These particulars are taken from the publications of Hamilton & McRae [19] and of Abbott [13] Evidence of iodine deficiency among people in Winnipeg has also been noted by Edward.[19]

The land areas surrounding the five Great Lakes lying across southern Ontario and the states of Wisconsin, Michigan, Ohio, Pennsylvania and New York in the north-eastern United States have long been recognized as notoriously goitrous Goitre literature abounds in references to the disease in this area, in both animals and man. Edward [19] observed it in the Japanese Prisoners of War Camp at Angler on the north shore of Lake Superior.

Sixty years ago, Springle [27] and Adami [11] recorded goitre, or "grosse gorge", as common throughout the Laurentian mountains of Quebec especially in the counties of Terrebonne, Berthier, and St Maurice. The disease was also frequent in the lower-lying country around Montreal at such places as Vaudreuil and Beauharnois More recently, Greenwald (personal communication to WHO, 1958) has expressed the opinion that goitre is probably still common in the Montreal area and along the St. Lawrence to at least eighty miles below Quebec. In a nutrition survey of the Indian people inhabiting the townships surrounding James Bay—the southern extension of Hudson Bay—undertaken by the National Committee on Community Health, small goitres were found in 5 3% of 728 subjects examined The majority were in young women (Vivian et al [28]) Since 1945 all salt sold through the Hudson's Bay Posts has been iodized Canada, as a whole, adopted compulsory iodization of table salt in 1949.[31]

In the Province of Newfoundland, goitre was observed but once only among 868 unselected people from St. John's and five outports, who were examined for clinical biochemical evidence of abnormalities due to defective nutrition (Adamson et al.[15]). The fact that consumption of fish is high no doubt accounts for iodine sufficiency in Newfoundland.

United States of America

Although in recent times goitre has been largely overcome through the increasing use of iodized salt, the disease is still recognized as a serious regional health problem in the USA Starr [59] reported in 1958 that among 4500 men in industry in southern California 7% had thyroid deficiency. Projecting these findings, he estimates that one million working men in the USA have hypothyroidism unbeknown to them or their physicians

Considered in broad outline, and geographically from east to west, the goitre centres of the USA are found throughout the whole length of the Appalachian range, in all states bordering on the Great Lakes, westward through North Dakota, and into the far western states of Montana, Idaho, Utah, Oregon and Washington where the incidence is particularly heavy.

The coastal valley of Bella Coola, 270 miles north-west of Vancouver, is also peculiarly sensitive to the disease. Other areas of considerable prevalence in British Columbia lie to the east and north-east of Vancouver. These are the valley of the Lower Fraser river, the town of Kamloops, around Lake Okanagan at Keremeos, Penticton and Vernon, and thence northwards, including such places as Armstrong, Enderby and Salmon Arm Farther east, goitre occurs in the neighbourhood of the Arrow Lakes and in the valleys towards the Selkirk Mountains. To the north there are centres in the Cariboo Mountains, at the town of Prince George, and all along the Grand Trunk Pacific Railway as far as Edmonton in Alberta.

In Alberta, Walker [29] has seen a great deal of goitre in a strip of territory running due south from Edmonton to the northern border of the United States Places affected are Leduc, Wetaskiwin, Lacombe, Eckville, Red Deer, Big Valley, Olds, Didsbury, Calgary, High River, Champion and Cardston It is also prevalent in the southern districts irrigated by the South Saskatchewan river from Lethbridge and Taber through Medicine Hat to Gull Lake

Another part of Alberta where goitre is fairly common lies to the north-west of Edmonton in the area drained by the upper waters of the Peace and Athabaska rivers, and including such centres as Sexsmith, Peace River and Barrhead An early account of goitre in this general area is given by Dr John Richardson,[24] surgeon and scientist on Franklin's famous expedition to the polar seas in the north-west of Canada between 1819 and 1822. " At Edmonton ", he notes, " the disorder attacks those only who drink the water of the river The inhabitants of Rocky Mountain House, sixty miles nearer the source of the river, are more severely affected than those at Edmonton, but at Carlton House, a considerable distance below Edmonton, the disease is known only by name " Other writers who refer to former and more recent occurrences of goitre around Edmonton and in the basins drained by the two branches of the Saskatchewan river are Simpson,[26] Hector,[20] and T H Whitelaw (personal communication to F J Shepherd [25])

In Saskatchewan there are accounts of goitre at Saskatoon According to Binning,[16, 17] a prevalence among schoolchildren of 12.3% in 1934 has been greatly reduced by the administration of iodine in various forms Goitre is also found farther south, in the country immediately surrounding the town of Regina Other centres are at Qu'Appelle, between Regina and Indian Head, at Bethune, Govan, Raymore, Cupar and Ituna, north of Regina, and in a strip of country running from Shaunavon eastward to Weyburn (Jackes [21])

Goitre studies of schoolchildren have been made at widely separated places in Manitoba At Dauphine, in the west of the province, 74% of the children were affected In the south, 21% of children at Morden had goitre. At Winnipeg the goitre rate was 50%, and in the towns of Birds Hill and

considerable extent in the coast towns of Oregon, exemplifying the fact that proximity to the sea does not necessarily guarantee freedom from the disease. Darby and his colleagues[35] found almost no goitre among the Navajo Indians scattered throughout the arid lands of north-eastern Arizona

The goitre situation in the Middle West—particularly in Ohio and Michigan—has greatly improved in recent years owing to the introduction of iodized salt and the official encouragement given to its use. Brush & Altland[32] have reviewed the results of thirty years of goitre prevention with iodized salt in this area Their survey carried out in four Michigan counties in 1951 showed a goitre rate of 1 4% in 53 785 students, compared with a rate of 38 6% in 65 537 students from the same counties examined in 1924 Similarly, in Ohio the problem of enlarged thyroid is not nearly so acute as it was 35 years ago A survey of 22 402 children in four Ohio counties, completed in the spring of 1954 (Hamwi[41]), showed only 4 05% with enlarged thyroids. This compares with a prevalence of 32 3% among 21 580 children examined in the same counties in 1925.

Some idea of the significance of goitre in the USA may also be gained from the medical examination records of registrants for military service during the Second World War Referring to the occurrence of thyroid disease among 13 million men examined up to January 1944, Rowntree[58] says that during peacetime all doubtful cases were considered significant, with the result that the rate was 5 per 1000, but, as manpower for the fighting forces became scarcer, only the more outstanding clinical pictures were labelled actual disease—a fact which resulted in a recorded rate of 0 6 per 1000 Hyperthyroidism, in both war and peace, was more frequent than hypothyroidism, he adds

Details of the US Public Health Service investigations quoted above are taken from Olesen[52, 53] Other authorities consulted are Adolph & Prochaska (Nebraska),[30] Altland & Brush (Michigan),[31] Cavanagh (Washington),[33] Daft (Michigan & Ohio),[34] Darby (Navajo Reserve),[35] Foote (lower San Joaquin Valley, California),[36] George & Flory (lower Rio Grande Valley, Texas),[37] Greenwald (West Virginia),[38] Greenwald (Ohio & West Virginia),[39] Grollman & Gryte (western North Carolina),[40] Hamwi et al (Ohio),[41, 42] Hull (Colorado),[43] Johnson (Kentucky),[44] Jordan & Canuteson (Kansas),[45] Kenyon, Kelly & Macy (Great Lakes),[46] Kimball (Ohio & Michigan),[47] Mahorner (southern states),[48] Mahorner & Barrow (Deep South),[49] Marine (Ohio),[50] Miller (Great Lakes),[51] Pennington (Kentucky),[54] Phillips (Texas),[55] Phillips (south-western Virginia),[56] Richards (Utah),[57] Rowntree (recruits),[58] Starr (southern California)[59]

Mexico

In the upper basin of the Rio Grande del Norte begins a great Central and South American zone of goitre comparable with the vast endemics

Except for isolated pockets of high incidence in Kansas—especially where it borders on Missouri—and in the New Orleans district of Louisiana, the great central plains are comparatively goitre-free, as also are the states on the Atlantic seaboard and the southern states of Mississippi, Alabama, Georgia and Florida

The first reliable index of the over-all prevalence of goitre in the USA resulted from the examination of 2 510 701 men drafted for military service during the First World War Nearly 12 000 men had simple goitre and 31 % of these were rejected because their necks were so large that the collar of the military tunic could not be buttoned around them. The frequency of the disease was greatest among recruits from the States of Washington, Oregon, Montana and Idaho in the north-west and from the region of the Great Lakes It was least in men drafted from the southern and Atlantic coast states and most frequently seen in those of Scandinavian origin

Later, between the years 1923 and 1929, systematic goitre surveys of *elementary schoolchildren were made in various states by the US Public* Health Service The results revealed a general distribution very much the same as that shown by the earlier military survey, except that whereas the examination of drafted men disclosed the highest incidence in the states of the Pacific North-West, the surveys of the Public Health Service indicated the greatest incidence to be in certain areas of the Middle West, that is, in Ohio, Indiana, Illinois, Michigan, Iowa, Wisconsin and Minnesota—states grouped around the Great Lakes

Goitre rates in these areas were found to be high. For example, in the town of Cincinnati (Ohio), 26 % of the boys and 40 % of the girls were classed as having simple thyroid enlargement In the State of Minnesota the endemic was even more severe, 41 % of boys and 70 % of girls from 13 different localities showing evidence of thyroid enlargement Conditic in Michigan and Wisconsin were no better, rates of 40 %, 60 %, 70 % and even 100 % were reported among boys and girls from certain localities in these states

Throughout the eastern states, although some moderately high percentages are recorded by the Public Health Service, there is on the whole much less goitre than there is around the Great Lakes and in the Far West The State of Connecticut gave rates of 7 % in boys and 29 % in girls, and Massachusetts 9 % in boys and 22 % in girls There is almost no goitre in territories east of the Blue Ridge Mountains Indeed, South Carolina is famed for the fact that her fruits and vegetables have a high iodine content and that, in consequence, goitre incidence there is negligible.

As regards the Far West, statistics collected by the Public Health Service in the State of Colorado revealed thyroid enlargement in 25 % of boys and 30 % of girls Utah is a notoriously goitrous state, very high rates being found in the locality of Salt Lake City. In Oregon, thyroid enlargement prevailed in 22 % of boys and 38 % of girls Goitre is endemic to a

More recent experience in Mexico[60] confirms the existence of very high goitre rates in certain provinces and has proved the prophylactic reliability of salt iodized with iodate instead of iodide. Stacpoole[63, 64] has devised a new salt-iodizing plant, capable of producing 5 tons per hour, expressly designed to serve local requirements in severely endemic areas. In his description of this process he gives an account of some of the difficulties encountered with producers and purveyors of salt during the installation and initial operation of the machine at Pinotepa Nacional, Jamiltepec, in the province of Oaxaca, where in some localities goitre affects 80%-90% of the population

Historical aspects of goitre in Mexico and Central America are dealt with by Greenwald.[61]

Central America

Since the establishment of the Institute of Nutrition of Central America and Panama (INCAP) in 1949, extensive surveys have been made to determine the prevalence of endemic goitre in Central America. As a result, it has been shown that the disease is a serious public health problem in Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica and Panama[65, 66, 67]

Guatemala

A survey made in 1938 by Herrera[70] confirmed earlier findings by Guerrero (1908) and by Díaz (1918) that goitre is a serious condition in Guatemala, affecting 50% of the people in some localities Dr Herrera established seven goitrous zones involving 16 departments: (1) Chimaltenango, Sacatepéquez, Sololá, the northern part of Escuintla and Suchitepéquez, and the southern part of Quiché as far as Totonicapán and Quezaltenango, (2) El Progreso and the south-west part of Zacapa, (3) the north-west part of Jutiapa and part of Jalapa, (4) the north-west of Quezaltenango and San Marcos; (5) the south of Huehuetenango; (6) the north-west of Huehuetenango, (7) the north-west of Santa Rosa The Department of El Progreso showed the highest prevalence

The most modern statistics are those compiled by Mahorner[73] and by Scrimshaw and his co-workers in INCAP[71, 75, 76] They have found an overall prevalence of 38 5% in the Departments of Guatemala, Escuintla, Chimaltenango and Sacatepéquez, some regions of which showed rates varying between 60% and 74% Interested also in the history of goitre, Borhegyi & Scrimshaw[68, 69] have marshalled evidence from archaeological and other sources pointing to the fact that goitre existed in Guatemala hundreds if not thousands of years before the conquest of the country by the Spaniards in 1524.

of the Alps and Himalayas It extends through Mexico and the Central *American Republics into Colombia and Venezuela, along the Cordillera* of the Andes through Ecuador and Peru as far as Chile and western Argentina

According to Stacpoole,[62] the greatest goitre authority in Mexico, endemic centres are found in all Mexican states bordering the Pacific except lower California Goitre also affects the mid-central and southern parts of the country The north-central gulf-coast of Tamaulipas and the Caribbean regions of Campeche, Yucatan and Quintana Roo are practically exempt Most of the goitre centres are situated in the mountains, but there are stretches along the Pacific coast where the disease is also to be found.

Up to the end of 1952, Stacpoole and two colleagues had examined more than one million children and adults in eight mid-central states, with a total population of over 10 million The results of the survey (see Table I)

TABLE I PREVALENCE OF GOITRE IN EIGHT STATES OF MEXICO

State	Total population	Cases of goitre	Prevalence (%)
Distrito federal	3 309 367	165 468	5
Puebla	1 691 950	406 066	24
Michoacán	1 470 837	385 359	26
México	1 443 681	425 886	30
Guerrero	952 037	261 811	27
Hidalgo	861 521	303 282	35
Morelos	291 119	135 661	46
Tlaxcala	290 592	108 972	37
Total	10 311 104	2 192 505	20

indicate that in these eight states there are more than two million people afflicted with goitre, that is, a rate of about 20% for the whole area

The survey covered 3756 towns and villages within 858 townships Rates of more than 80% were common in many places and in some communities upwards of 90% of the population were found to be goitrous.

According to law, all municipalities in which more than 20% of the population are affected by goitre are obliged to use iodized salt exclusively, and energetic measures are being taken to overcome the administrative difficulties that prevent enforcement of the law Since 1950 prophylaxis by means of iodized sweets has been carried out among 50 000 children in 45 schools in the Federal District and in 80 schools in the State of Morelos. The result has been an average drop of 16% in goitre prevalence among children in these schools

goitrous people out of a total population of 1 856 000 (Cabezas, Pineda & Scrimshaw [65])

Nicaragua

An examination of 2427 children carried out in 1954 under the auspices of INCAP gave the results shown in Table II (N. S Scrimshaw—personal communication, 1954).

TABLE II CASES OF GOITRE AMONG CHILDREN IN NICARAGUA

Department	District	Number of children examined	Number with goitre	Percentage with goitre
Carazo	Santa Teresa	157	85	54 1
"	Diriamba	223	44	19 7
"	Jinotepe	438	57	13 0
Masaya	Nindiri	90	20	22.2
"	Masaya	224	32	14.3
Managua	San Rafael del Sur	117	62	53 0
"	El Salto	51	23	45 1
"	Las Maderas	72	28	38.9
"	Montelimar	47	12	25 5
"	Managua	457	98	21 4
"	Tipitapa	35	1	2 9
Matagalpa	Matagalpa	355	81	22.8
	C Dario	161	7	4 4
	Total	2 427	550	22 6

These statistics indicate an average goitre rate of 22 6% In the districts of Santa Teresa (Carazo) and San Rafael del Sur (Managua) the rate exceeds 50%

Costa Rica

Goitre statistics for Costa Rica are few, but they are sufficiently disquieting to justify the official introduction of preventive measures. Garcia [85] found a rate of 10 6% among male patients in a mental hospital. He also refers to a series of 1000 autopsies in which 45 goitres were noted Investigations in the canton of Puriscal by Urcuyo [87] revealed 27 cases of thyroid abnormality among 1000 people examined ; 6 of these cases were in men and 21 in women

Nodular goitres are common in the highlands of Guatemala, by contrast, nodular goitres are uncommon in El Salvador. Deaf-mutism and idiocy are frequently found in association with iodine deficiency in the highly endemic areas of Guatemala These sequelae were not observed in El Salvador Writing of conditions in Guatemala as he encountered them in 1950, Kimball[72] says: "I have never seen such degeneration; feeblemindedness and deafmutism were very frequent"

Energetic official action is being taken to combat goitre in Guatemala by means of iodized salt Both iodate and iodide in doses of equivalent *iodine content have been tested and found equally effective. Experiments* on Guatemalan children reported by Scrimshaw and his colleagues[74, 77] show that after 32 weeks of treatment the goitre rate was reduced from 51% to 16% with iodate, and from 60% to 23% with iodide

Honduras

In common with most other Central American countries the over-all prevalence of goitre in Honduras is high As part of the INCAP goitre survey, Borjas and Scrimshaw[78, 79] examined a total of 12 292 schoolchildren and 352 adults, comprising nearly 1% of the population in all 15 departments, and found that nearly one-fourth (22.6%) of these people had pathologically enlarged thyroid glands Slightly less than 14% of the goitres were readily visible with the head in normal position and fewer than 1% had discrete nodules The highest rates occur in the Ajuterique and Lejamani districts of the Department of Comayagua (73% and 74% respectively) and in the La Venta area of Morazán Department (64%).[71]

El Salvador

Goitre is endemic in all 14 departments of El Salvador.[81] During 1952 nearly 35 000 schoolchildren of all ages from public and private schools in urban and rural areas were examined by a goitre survey team under the auspices of INCAP. Glands were not considered enlarged unless they were definitely four to five times the "normal" size[65, 80, 82]

Of 8000 children examined in the capital (San Salvador) only 1.1% were found to have thyroids more than four to five times the normal size Among the 26 400 children examined in the remainder of the country the average rate was 22.8%, with variations between 8.5% and 38 7%, depending on the department. Deaf-mutism, idiocy and cretinism were not observed The worst affected department was Ahuachapán.

On the basis of these studies, it is calculated that 119 000 children in El Salvador out of a total school population of 673 000 are affected with goitre. If these average figures for schoolchildren can be taken as reasonably representative of the population as a whole, El Salvador would have 329 000

ages of 10 and 14 years, are especially prone to the disease. The condition is accompanied by under-development, sexual immaturity, idiocy and cretinism. Sterility and other manifestations of reproductive failure are common among women. The goitre seen in these areas is characteristically benign; toxic phenomena are never seen. La Pelada, El Salto, Manabao, Pinarquemado, Boma, La Peña and Vera Bellica are the most affected sections in this area. If iodine treatment is applied in childhood excellent results are obtained. Nothing can be done medically to alleviate goitres in patients over the age of 20 years

South America

From earliest times the continent of South America has presented a fruitful field of study for the goitre investigator. Crotti [47] recounts how the first explorers of New Granada (now Colombia) were astonished to find the banks of the Rio Magdalena inhabited by a race of " heavy and stupid savages of sluggish habit who passed their days in sleep " Among the goitrous Indians of the Peruvian plateau, cretinism had reached such a degree in those days that it required nothing less than a papal bull from Paul III (*d.* 1549) to convince the missionaries that these were indeed men with souls to be evangelized. On the other hand, painstaking historical research has convinced Greenwald [58] that goitre was unknown in the Inca Empire and did not appear there (i.e., in Colombia, Ecuador, Bolivia, Peru, Chile and Argentina) until after the Spanish conquest of these countries This is in line with the views of Bengoa [117]

Today, the disease is found in almost every country of South America Summaries of the history, prevalence and geographical distribution of goitre in South American countries up to the year 1950 have been made by the Chilean Iodine Educational Bureaux of London and Santiago.[2, 3] Orr [99] and Kimball [72] are two other authorities who have written interesting general accounts of goitre in South America

Colombia

Endemic goitre in Colombia is a problem of long standing. Mutis [110] reported in 1794 that he had seen goitrous people on the upper Magdalena River in 1760, that is, more than thirty years prior to the date of the written record. In 1797 Gil de Tejada [103] wrote about the cause and cure of the disease in Santafé (Bogotá) Francisco José de Caldas, noted Colombian naturalist and patriot, repeatedly mentions goitre in his writings (1808) Apparently he was the first to attribute the disease to the quality of the local drinking-waters—some excessively charged with lime and others with calcium sulfate, iron, and decaying vegetation. About the same time (1810) Camacho studied the distribution and extent of the Colombian endemic and observed that the disease was frequent in the convents of

More recent surveys by INCAP (N S Scrimshaw—personal communication, 1954) revealed an average rate of 12% among 24 000 children examined The following are the figures for five of the seven provinces: Alajuela, 17%; Cartago, 12%; Heredia, 15%; Limón, 6%; San José, 8%.

Lack of iodine in drinking-water, monotonous diet, and hardness of water are considered by De Girolami & Fallas Díaz[84] to be the causes of the Costa Rican endemic Cases of cretinism and deaf-mutism are of sporadic occurrence

Panama

The Peruvian expert, Dr Arce Larreta, examined a total of 3540 persons in the Province of Chiriquí as part of the INCAP survey[71] He found goitre rates as follows 2 5% in children up to 6 years of age (808 examined); 50% in children of school age (1682 examined); and 75% in adults of 18 years or over (1050 examined)

More recently Reverte Coma[88 91, 93] has carried out extensive goitre surveys throughout Panama In Herrera and Chame the following percentage prevalences were noted

	Pre-school children	*Schoolchildren*	*Adults*
Herrera	6 80	60 81	46 85
Chame	1 05	21 18	17.81

Many cases of cretinism and deaf-mutism were found. Reverte Coma[92] has also studied the " Anne Boleyn " syndrome, the name given by Marañon and his school to the simultaneous existence of goitre and polydactylism in a patient He estimates that cases of polydactylism on the Panama Isthmus number 1 in every 2000 or 3000 inhabitants, the majority being from areas where goitre is endemic

Cuba

Zones of endemic goitre do not apparently exist in Cuba Nevertheless, sporadic cases occur with more than usual frequency in the regions of Sagua de Tánamo, Morón, and Ciego de Avila. Three of these, all in one family, have been described by Schutte et al[94]

Dominican Republic

According to Purcell[96] numerous cases of simple goitre are found in Santo Domingo. He mentioned El Cerado, El Pinar, Los Arroyos, El Coco and Los Naranjos as the districts most affected.

De León[95] refers to the frequency of goitre among the country people in the mountainous zone of Jarabacoa Women, and children between the

ages of 10 and 14 years, are especially prone to the disease The condition is accompanied by under-development, sexual immaturity, idiocy and cretinism. Sterility and other manifestations of reproductive failure are common among women. The goitre seen in these areas is characteristically benign; toxic phenomena are never seen. La Pelada, El Salto, Manabao, Pinarquemado, Boma, La Peña and Vera Bellica are the most affected sections in this area. If iodine treatment is applied in childhood excellent results are obtained Nothing can be done medically to alleviate goitres in patients over the age of 20 years

South America

From earliest times the continent of South America has presented a fruitful field of study for the goitre investigator. Crotti [97] recounts how the first explorers of New Granada (now Colombia) were astonished to find the banks of the Rio Magdalena inhabited by a race of " heavy and stupid savages of sluggish habit who passed their days in sleep." Among the goitrous Indians of the Peruvian plateau, cretinism had reached such a degree in those days that it required nothing less than a papal bull from Paul III (*d* 1549) to convince the missionaries that these were indeed men with souls to be evangelized On the other hand, painstaking historical research has convinced Greenwald [98] that goitre was unknown in the Inca Empire and did not appear there (i.e., in Colombia, Ecuador, Bolivia, Peru, Chile and Argentina) until after the Spanish conquest of these countries This is in line with the views of Bengoa.[117]

Today, the disease is found in almost every country of South America Summaries of the history, prevalence and geographical distribution of goitre in South American countries up to the year 1950 have been made by the Chilean Iodine Educational Bureaux of London and Santiago [2, 3] Orr [99] and Kimball [72] are two other authorities who have written interesting general accounts of goitre in South America

Colombia

Endemic goitre in Colombia is a problem of long standing Mutis [110] reported in 1794 that he had seen goitrous people on the upper Magdalena River in 1760, that is, more than thirty years prior to the date of the written record In 1797 Gil de Tejada [103] wrote about the cause and cure of the disease in Santafé (Bogotá). Francisco José de Caldas, noted Colombian naturalist and patriot, repeatedly mentions goitre in his writings (1808). Apparently he was the first to attribute the disease to the quality of the local drinking-waters—some excessively charged with lime and others with calcium sulfate, iron, and decaying vegetation. About the same time (1810) Camacho studied the distribution and extent of the Colombian endemic and observed that the disease was frequent in the convents of

More recent surveys by INCAP (N S Scrimshaw—personal communication, 1954) revealed an average rate of 12% among 24 000 children examined The following are the figures for five of the seven provinces: Alajuela, 17%; Cartago, 12%, Heredia, 15%; Limón, 6%; San José, 8%.

Lack of iodine in drinking-water, monotonous diet, and hardness of water are considered by De Girolami & Fallas Díaz [81] to be the causes of the Costa Rican endemic. Cases of cretinism and deaf-mutism are of sporadic occurrence

Panama

The Peruvian expert, Dr Arce Larreta, examined a total of 3540 persons in the Province of Chiriquí as part of the INCAP survey [71] He found goitre rates as follows: 2 5% in children up to 6 years of age (808 examined); 50% in children of school age (1682 examined), and 75% in adults of 18 years or over (1050 examined)

More recently Reverte Coma [88-91, 93] has carried out extensive goitre surveys throughout Panama In Herrera and Chame the following percentage prevalences were noted.

	Pre-school children	*Schoolchildren*	*Adults*
Herrera	6 80	60 81	46 85
Chame	1 05	21 18	17 81

Many cases of cretinism and deaf-mutism were found Reverte Coma [92] has also studied the " Anne Boleyn " syndrome, the name given by Marañon and his school to the simultaneous existence of goitre and polydactylism in a patient He estimates that cases of polydactylism on the Panama Isthmus number 1 in every 2000 or 3000 inhabitants, the majority being from areas where goitre is endemic

Cuba

Zones of endemic goitre do not apparently exist in Cuba. Nevertheless, sporadic cases occur with more than usual frequency in the regions of Sagua de Tánamo, Morón, and Ciego de Avila Three of these, all in one family, have been described by Schutte et al [94]

Dominican Republic

According to Purcell [96] numerous cases of simple goitre are found in Santo Domingo He mentioned El Cerado, El Pinar, Los Arroyos, El Coco and Los Naranjos as the districts most affected.

De León [95] refers to the frequency of goitre among the country people in the mountainous zone of Jarabacoa. Women, and children between the

Bogotá, where well water of exceptional hardness was used for drinking and cooking purposes (Socarrás [115]).

A special interest attaches to the story of goitre in Colombia because it was there that the famous French scientist, J B Boussingault,[100, 101] put forward for the first time (1831) the recommendation that domestic salt supplies should be iodized to prevent goitre The circumstances are these In 1824 von Humboldt [109] described the occurrence of goitre in the Andean plateau and referred to the striking fact that the inhabitants of goitrous localities recognized that salt from certain natural deposits was more beneficial than that from others The following year, a young doctor named Roulin, [114] who had recently come to Colombia from Paris full of information and ideas about Coindet's new iodine treatment of goitre,[3] noted this and was instrumental in having samples of the salts analysed by Boussingault. On analysis Boussingault made the significant discovery that those salts instinctively preferred by the goitrous peoples contained most iodine. This prompted his recommendation

Although almost 130 years have passed since Boussingault's advice was given, it is only recently that active steps have been taken to stamp out, by means of iodized salt, the serious degree of goitre which is still found throughout almost the whole length of the valleys of the Magdalena and Cauca rivers The decision to introduce iodized salt has been taken as a result of several new and detailed goitre surveys

The first of these inquiries, published by Socarrás [115] in 1942, showed that 10% of 153 000 prospective recruits for military service examined over a period of five years were rejected because of simple goitre In January 1945, the Department of Nutrition of the Co-operative Health Service (Servicio Cooperativo Interamericano de Salud Pública) began a four-year survey of the geographical distribution and frequency of simple goitre among schoolchildren from 7 to 14 years of age throughout the entire country. Few, if any, more complete surveys of this kind have ever been made anywhere in the world The results, published in summary form by Parra [111 113] and in great detail by Góngora y López, Young & Iregui,[107] are shown in Table III They cover 183 243 children in 14 departments and show an average goitre rate of 52 62%, the highest figure being 81 14% for the Department of Caldas

Commenting on this survey Parra [111 112] mentions that the departments with the lowest goitre rates (Atlántico, Bolivar and Magdalena) border on the sea coast, where there is a higher consumption of foods of marine origin He also refers to the fact that during the last thirty years simple goitre has been invading areas formerly untouched by it, e g , the Departments of Caldas and Antioquia This is because the regional supply of salt from iodized sources has gradually been almost completely replaced by cheaper salt of extremely low iodine content from large mines near Bogotá Another interesting conclusion drawn from the survey is that in

FIG 2 SOUTH AMERICA



The red hatching indicates the areas where endemic goitre has been found

Bogotá, where well water of exceptional hardness was used for drinking and cooking purposes (Socarrás [115])

A special interest attaches to the story of goitre in Colombia because it was there that the famous French scientist, J B Boussingault,[100, 101] put forward for the first time (1831) the recommendation that domestic salt supplies should be iodized to prevent goitre The circumstances are these In 1824 von Humboldt [109] described the occurrence of goitre in the Andean plateau and referred to the striking fact that the inhabitants of goitrous localities recognized that salt from certain natural deposits was more beneficial than that from others The following year, a young doctor named Roulin, [114] who had recently come to Colombia from Paris full of information and ideas about Coindet's new iodine treatment of goitre,[3] noted this and was instrumental in having samples of the salts analysed by Boussingault. On analysis Boussingault made the significant discovery that those salts instinctively preferred by the goitrous peoples contained most iodine This prompted his recommendation

Although almost 130 years have passed since Boussingault's advice was given, it is only recently that active steps have been taken to stamp out, by means of iodized salt, the serious degree of goitre which is still found throughout almost the whole length of the valleys of the Magdalena and Cauca rivers The decision to introduce iodized salt has been taken as a result of several new and detailed goitre surveys

The first of these inquiries, published by Socarras [115] in 1942, showed that 10% of 153 000 prospective recruits for military service examined over a period of five years were rejected because of simple goitre In January 1945, the Department of Nutrition of the Co-operative Health Service (Servicio Cooperativo Interamericano de Salud Publica) began a four-year survey of the geographical distribution and frequency of simple goitre among schoolchildren from 7 to 14 years of age throughout the entire country. Few, if any, more complete surveys of this kind have ever been made anywhere in the world The results, published in summary form by Parra [111 113] and in great detail by Góngora y López, Young & Iregui,[107] are shown in Table III They cover 183 243 children in 14 departments and show an average goitre rate of 52 62%, the highest figure being 81 14% for the Department of Caldas

Commenting on this survey Parra [111, 112] mentions that the departments with the lowest goitre rates (Atlántico, Bolivar and Magdalena) border on the sea coast, where there is a higher consumption of foods of marine origin He also refers to the fact that during the last thirty years simple goitre has been invading areas formerly untouched by it, e g , the Departments of Caldas and Antioquia This is because the regional supply of salt from iodized sources has gradually been almost completely replaced by cheaper salt of extremely low iodine content from large mines near Bogotá Another interesting conclusion drawn from the survey is that in

FIG 2 SOUTH AMERICA



The red hatching indicates the areas where endemic goitre has been found

Among those who have made recent contributions to knowledge of Colombian goitre are Gomez-Afanador [104] who in a series of 244 cases found 82% to be simple goitres, 10% hypothyroid and 8% hyperthyroid; Thonnard-Neumann [116] who refers to the goitre problem in his assessment of the poor nutritional status of the Colombian people; and Correa & Castro [102] who describe the natural history of the disease in Cali.

Venezuela

From the Rio Magdalena in Colombia the goitre belt extends eastwards into Venezuela through the basins of the Meta and Apure rivers, and more particularly along the Cordillera of Mérida, affecting such places as Pamplona, La Grita, Tovar, Mérida, Trujillo and Barquisimeto, and continuing as far as Valencia and Caracas

The most authoritative account of endemic goitre in Venezuela is contained in the comprehensive health survey of that country by Bengoa.[117] He is of the opinion that goitre did not exist in Venezuela prior to the colonization, owing to the typical nomadic tendencies of the indigenous tribes of the Caribbean countries. When the people began to live in settled communities, however, goitre began to develop. Indeed, Bengoa refers to the tradition that from the time of colonization practically everybody in Trujillo was goitrous, a fact which in those days marked out foreigners and people without goitre as rare individuals

The intensity of the goitre endemic in several towns of the Republic is seen in the following tabulation, which shows the percentage rates among students examined in the year 1941

Locality	*Goitre rate (%)*	*Locality*	*Goitre rate (%)*
La Grita	47	Pregonero	12
Guarico	28	Cuicas	11
Monte Carmelo	25	Tovar	5
Chejendé	18	Carvajal	2
Merida	13	Campo Elias	2
Biscucuy	12	Mucuchies	1

These rates are for cases of *obvious* goitre. Bengoa, [117] from whose book the data are taken, says that only isolated cases of cretinism and deaf-mutism are encountered, and that the goitre problem in Venezuela as a whole does not have the same serious social significance as in some other South American countries Nevertheless, he commends it to the notice of official public health authorities, with the proposal that iodized salt should be introduced to diminish the present intensity of the condition.

Heedful of this red light, the Instituto Nacional de Nutrición organized a series of field surveys and laboratory studies in 1951 which confirmed the high goitre rates existing along the Venezuelan Andes and foothills from San Cristóbal at the southern end of the ridge through Trujillo,

TABLE III PREVALENCE OF SIMPLE GOITRE AMONG COLOMBIAN SCHOOLCHILDREN, 1945-48

Department	Children examined	Positive cases	Percentage
1 Antioquia	20 038	9 374	46.73
2 Atlántico	4 425	1 012	22 64
3 Bolivar	8 097	2 333	28 81
4 Boyacá	8 025	4 691	58 45
5. Caldas	25 280	20 511	81 14
6 Cauca	6 234	4 960	79 56
7 Cundinamarca	34 665	15 909	45 83
8 Magdalena	5 572	1 364	24 47
9 Huila	6 137	4 246	69 18
10 Nariño	12 892	4 844	37 57
11 Norte de Santander	4 130	1 684	40 77
12 Santander	10 523	4 993	47 45
13 Tolima	10 941	6 635	60 64
14 Valle del Cauca	26 264	13 879	52.84
Total	183 243	96 435	52 62

places with soft or semi-hard water the goitre incidence is less than in localities where the water is hard or very hard.

Where the endemic has been of long duration—100 years or more—the physique of the people is substandard and there are evidences of retarded mental development and of cretinism

Goitre preventive measures involving the iodization of the salt supply for the entire country have been given official sanction, and Góngora y López & Young [106] have given a full description of the approved process for iodizing the salt produced from the natural deposits found at Zipaquirá.

The average daily intake of salt per head is said to be 15 g, and the level of iodization adopted is 1 part of iodine in 25 000 parts of salt. That iodized salt is effective in reducing the degree of goitre in young Colombian children is already evident from the results of a two-year trial recorded by Góngora y López & Mejia.[105] Beginning in May 1950, a total of 8062 children from seven different localities in the Department of Caldas were given iodized salt regularly As controls, 797 children from two other zones in Caldas and 1648 children from the city of Bogotá were given no iodized salt. At a resurvey in April 1952 the number of cases of goitre in the iodized salt group had diminished by 57.6% compared with the rates obtaining in 1945-48. The goitre rate among the children not getting iodized salt was the same in 1952 as was found in the 1945-48 survey.

and half-castes are most vulnerable to the disease because of their extreme poverty and poor nutritional status This coincides with the opinion of Arcos, who maintains that goitre persists in the rural areas of Ecuador, particularly in the narrow Andean valleys, owing to low standards of living and the lack of adequate medical and social services Arcos confirms that the disease is very extensive in the Province of Cotopaxi (formerly called Léon), especially among Indian races. He thinks, too, that thyroid deficiency is the greatest single cause of decadence among these peoples.

Precise statistics are not available in respect of the Ecuadorean population; but it is believed that goitre affects both sexes equally It is particularly evident at puberty and adolescence Thyroid enlargement is also known to occur among domestic animals in Ecuador (Sánchez & Paredes [132]) Horses, pigs and lambs are affected

An exhaustive review of the history and folklore of endemic goitre in Ecuador is given by León [131] He refers to the occurrence of the disease in the times of the Inca Empire, when it was known by the Quichua term *ccotto* or *coto* meaning a mound or protuberance, and traces its development during and after the Spanish colonial era The frequency of goitre throughout the Ecuadorean highlands has not only had its repercussions on the medical, biological and social life of the people, but has also influenced the national plastic and pictorial arts

Peru

Although goitre, cretinism and deaf-mutism have long been a burden on public health in Peru, only recently have medical officials been able to convince the Government of the preventive possibilities in iodized salt and the need to make its use compulsory The Ministry of Public Health in Peru has now organized a campaign for the prophylaxis of endemic goitre by means of salt iodized at the rate of 1 part of iodine in 10 000 parts of salt

The location and intensity of the present-day endemic in Peru was first clearly defined by Salazar [143] in a series of maps, on which occurrence is plotted department by department Most affected are those departments covering the central higher parts of the country Moving from north to south, the following are the ten departments with the highest rates: Amazonas (28 79%), Cajamarca (3 63%), Libertad (6 38%), Ancash (14 36%), Huánuco (19 96%), Junin (5 09%), Huancavelica (8.77%), Ayacucho (4 28%), Apurímac (9 88%) and Cuzco (4 92%) Cases of goitre in the remaining 13 departments of the country occur in 2% of the population or less.

Burga,[134, 135] who is in charge of the Peruvian goitre campaign, has drawn special attention to the differences between goitre conditions in different parts of the Department of Amazonas There, the goitre rate in low-lying areas—namely, 90%—is much greater than in the higher parts of the Department, and cretinism, mental deficiency and deaf-mutism are

Tocuyo and the Carabobo area almost as far as the non-goitrous zone of Caracas For instance, in the county of Bailadores in the state of Mérida 84.5% of 718 adults and 83% of 641 schoolchildren examined by Roche et al [124 125] were found to have abnormally palpable thyroids Garcia [122] encountered rates of between 22% and 96% among groups of men, women and children from different localities in Palmira and Piñango, two districts situated in the mountainous region to the north-east of Mérida between the states of Zulia and Trujillo In Manuare valley (Carabobo state) Rodriguez [128, 129] records an incidence of 36 3% in the 381 persons he examined, almost 16% of the total population of the district

Radioiodine clearance has been studied by Roche and his colleagues on the inhabitants of the mountainous regions of Bailadores and Tabay in the far-west of the country and on goitre subjects from Manuare and San Joaquin in the state of Carabobo [118 121, 126 127]

Some 500 miles to the south-east, Roche [123] made similar investigations in the savanna of Kakuri near the sources of the Ventuari river in the Amazon territory of Venezuela Here, the 24-hour thyroidal uptake of ^{131}I was measured in 53 well-nourished Indians who had had little or no contact with white men and who, with one exception, had thyroids that were either non-palpable or normal in size The average ^{131}I uptake was 70 8% of the administered dose, 45 of the cases had uptakes of more than 50% of the dose Uptakes of six controls, members of the expedition, were within normal limits If it be assumed that the demonstrated thyroidal avidity for iodine signifies iodine deficiency, the findings would suggest that such deficiency may exist without giving rise to the symptom of goitre

Ecuador

From Colombia, the South American goitre zone passes southwards along the Cordillera into Ecuador, touching such centres as Quito, Cuenca and Loja.

More than 120 years ago, von Humboldt (1824) [109] and Boussingault (1833) [101] mention goitre as being endemic in Ecuador. In Llano Anciso a case was seen in which the swelling was 14 inches (36 cm) long and 8 inches (20 cm) across Although this is exceptional, conditions predispose to the appearance of such phenomena There are one or two areas, however, where goitre does not occur because the local sources of food salt are *sufficiently rich in iodine*

In recent years the Ecuadorean goitre problem has been carefully studied by Sánchez & Paredes [132] and by Arcos.[130] Sánchez & Paredes state that most goitre is found in the central Andean spine running lengthwise through the middle of the country. The littoral zone to the west and the upper Amazonian area on the east side—both of which are comparatively low-lying—are less affected. These authors claim that the native Indians

Department of Santa Cruz, in the east of the country. Similarly, in Tacuarembotí and in Tarija, where goitres are very abundant, the words "cotudos" and "cotos" are in common use to describe the peoples there. (See also León [131] under Ecuador)

Worthy perhaps of passing mention is the local belief in certain places in Bolivia that goitre co-exists with an abundance of alder trees which, so it is conjectured, absorb all iodine from the soil and render it iodine-deficient.

Exact numerical statistics are not available but, from his personal observations, Balcazar has assigned the following degrees of prevalence to eight of the nine departments of the country, arranged in order as nearly as possible from north to south. He says that over-all rates of 40% or more are not uncommon in some provinces.

Beni Very abundant, especially in the Provinces of Cercado and Vaca Diez, and in parts of Itéñez

Santa Cruz Abundant. A rate of 17% among schoolchildren in the capital city. Many cases in the Provinces of Valle Grande, Chiquitos and Cordillera

La Paz Low incidence in the Yungas Provinces, but very prevalent in practically all the others. Very common in the peninsula of Copacabana (Lake Titicaca).

Cochabamba Frequent in many provinces Abundant in Independencia, the capital of Ayopaya Province. Grave foci in Pasorapa, Toyota and Emereque

Oruro Sporadic cases in several cantons

Potosí An extraordinary number in Millares Many cases in Tacobamba, Ancoma and Potobamba Grave foci in Condes and frequent cases in many other places.

Chuquisaca Zudáñez Province is wholly goitrous. Many other places affected.

Tarija. Very prevalent Main foci are in the capital and in the Provinces of Cercado, Méndez, Avilés, Arce and O'Connor.

The goitre problem in Bolivia is bound up with lack of education, poor housing, deficient nutrition, generally low standards of living and the *prevalence of venereal disease, alcoholism and indulgence in coca*

The Bolivian Government plan to iodize all food salt used throughout the country and to ensure this end propose to create a salt monopoly

Chile

Compared with other South American republics, Chile is not a goitrous country. During his travels from Argentina over the Andes into and throughout Chile in the years 1820 and 1821, Schmidtmeyer [163] especially noted that "the inhabitants of Santiago, however, do not exhibit the same

correspondingly serious. The drinking-water is from streams. In the highlands, on the other hand, Burga found a rate of 30%, mostly among adolescents. Here the water-supply comes from wells. Goitre in newborn babies is common, and the disease is also seen in domestic animals, particularly dogs

In later and more comprehensive surveys covering the whole of Peru, Burga [138] has confirmed his *earlier opinions, namely, that serious endemic* goitre is confined to the region of the Sierra, that it is not found on the coast, and that in the rising and foothill country between these two zones the disease has an *intermediate severity, being wholly absent in some localities.*

Burga's studies relating prevalence to altitude are among the best in the goitre literature Moving inwards from the coast to an ascent of the Cordillera one first encounters cases of goitre at 250-850 metres above sea-level; at an elevation of 1000-3000 metres the frequency increases, attaining average rates of 15% to 25% and above. At this level, the disease is characterized by the presence of cretinism, myxoedema, and a general state of hypometabolism extending also to domestic animals. At an even greater height, over 3300 metres, the goitre rate tends to diminish again, until it recedes to an almost insignificant figure in places of highest altitude. In these zones, cretins and cases of myxoedema are rarely seen and it is difficult to find any animals with thyroid enlargement. These conclusions of Burga and his team [138, 142] are based on the examination of many thousands of men, women and children in 84 provinces of 14 districts of Peru

A feature mentioned by Monge [141] is the unusually large size of the goitres found in Urubamba Province near the town of Cuzco in the southern part of Peru It appears, too, that toxic goitre (Basedow's syndrome) is not uncommon in this area

Those interested in historical aspects of goitre in Peru are commended to the writings of Lastres [139, 140] and of Greenwald & Lastres.[137]

Bolivia

Our knowledge of the distribution of goitre in Bolivia is due, in the main, to the modern investigations of Balcazar,[145] Fernández,[146] and Ibáñez.[147]

As with other South American republics, records of the Bolivian endemic are several centuries old Following the Spanish conquest of the Incas early in the sixteenth century and the reorganization of the country as a dependency of the Viceroyalty of Peru, known politically as the Audiencia of Charcas, Viceroy Francisco de Toledo (1569-1581) sent a commission of " empiricists " from his seat of government at Sucre to Zudáñez, capital of the province of the same name in the Department of Chuquisaca, to cure the goitre there, so serious had it become.

Significant, too, is the fact that the Bolivian word for goitre, " coto ", has given rise to the place-name Cotoca, a township in Cercado Province,

TABLE IV PERCENTAGE OF THYROID ENLARGEMENT AMONG SCHOOLCHILDREN IN THE VARIOUS DISTRICTS OF THE SIX DEPARTMENTS OF THE PROVINCE OF SANTIAGO, AND OF THE SIX DEPARTMENTS OF THE PROVINCE OF COQUIMBO, CHILE

Department and district	Percentage with enlarged thyroid	Department and district	Percentage with enlarged thyroid
Province of Santiago			
Santiago		**Talagante**	
Lampa	22	Isla de Maipo	15
Til-Til	25	Talagante	13
Quilicura	13	Peñaflor	5
Curacaví	38	**Maipo**	
Maipú	5	Paine	25
Florida	3	Buin	27
Renca	7	**San Antonio**	
Colina	25	Cartagena	0
Puente Alto	19	San Antonio	1
La Granja	23	Santo Domingo	13
Pirque	32	Navidad	11
San J de Maipo	37	**San Bernardo**	
Conchali	10	Calera de Tango	21
San Miguel	4	San Bernardo	15
Cisterna	5	**Melipilla**	
Las Condes	10	El Monte	8
Quinta Normal	5	Melipilla	14
Nuñoa	0	Alhué	36
Providencia	6	María Pinto	13
Barrancas	12	San Pedro	3
Santiago	6		
Province of Coquimbo			
La Serena		**Ovalle**	
La Serena	4	Ovalle	14
La Higuera	1	Monte Patria	20
Elqui		Punitaqui	30
Vicuña	3	Samo Alto	34
Paihuano	2	**Combarbala**	
Coquimbo		Combarbala	27
Coquimbo	2	**Illapel**	
Andacollo	21	Illapel	17
		Salamanca	38
		Los Vilos	9

enlargement of the neck and head as the Mendozines: . . . I observed it in women inhabiting cottages within a few leagues of Santiago, and in the midst of irrigated grounds, but nowhere else in Chile during a journey of above a thousand miles, along both the sea shore and the foot of the Andes." Strain [161] also came across only a few isolated cases on his journeys through Chile in 1849; he was told by the people whom he met that goitre was unknown in Chile until about 20 years before that time, when, according to tradition, the disease made its appearance simultaneously with the introduction of the Italian poplar tree from Mendoza. Gilliss,[159] another traveller, writes in much the same sense.

On the other hand, there are those who believe that the disease prevailed to a considerable extent in the colonial era, but has largely declined with improved conditions and the advance of time Romero [162] says that in Santiago during the sixteenth century a connexion existed between the prevalence of goitre among the aristocracy and the fact that they had their own private sources of highly purified drinking-water, whereas the poorer people obtained water from relatively impure public supplies Fashionable painters of the time performed marvels in disguising the goitres of ladies who commissioned them to paint their portraits; elegance decreed the use of ribbons of black velvet around the neck and other aids to concealment. Some men, less concerned perhaps, allowed an unaesthetic and considerable tumour to show above the neckerchief.

Places considered to be mildly goitrous today lie in the area watered by the Aconcagua river, particularly around Los Andes and San Felipe P. Martini (cited by Romero [162]) of Los Andes mentions having seen goitre on the mountain road through the Cordillera to Juncal in Argentina Feferholtz & Ortiz [158] say that goitre is especially prevalent in Boco near Quillota, which is to the north-east of Valparaiso

Farther south, cases are occasionally found along the valleys of the Maipo and Cachapoal rivers, and at La Punta, a settlement just north of Rancagua in O'Higgins Province (Cabello & Zúñiga;[150] Zúñiga [166]) In this neighbourhood, also, goitre has been noted at Doñihue. At Teno near Curico, Alvarez [149] records a series of 111 cases, of which only 2 were men. He also observed a number of cretins and dwarfs. There are no established foci of endemic goitre in the Concepción area Suazo Figueroa [165] examined the reports of nearly 2500 biopsies and autopsies and found indications of the disease in only 45 persons (i.e , 1 8%), of whom 8 were men

The most recent and most comprehensive surveys are those carried out by Donoso and his colleagues [155, 153 157] on 39 433 schoolchildren distributed over 287 schools in the six departments of the Province of Santiago, and on 8332 pupils belonging to 119 schools in the six departments of the Province of Coquimbo. The over-all goitre rate in these two provinces is 10%-11%; but, as Table IV shows, rates of 20%, 30% and nearly 40% are the rule in some districts

23% for the whole province, with a maximum figure of 33.5% in Chichigasta. Statistics (1939-45)[171] for Catamarca record a rate of 100% in a school at Andalgalá; and Lobo and his colleagues found 32.68% of goitre in 1500 children examined in La Rioja schools.

According to a 1937 census of schools in 16 different places in Mendoza,[170] goitre rates varied from 28% to 88% among young children, the average rate being 43.5%. In subsequent studies, Perinetti and collaborators[185, 186] found 24 150 cases of thyroid enlargement among 52 548 children examined (i.e., 46%). Of these, 60% were palpable goitres, 36% visible, and 4% nodular. Data of a similar kind are available for the Territory of Formosa and the Provinces of Corrientes and Misiones, in all of which goitre frequencies of the order of 50% and above are found among children of school age.[167, 181, 182, 190]

Analytical researches by Mazzocco and Arias Aranda,[177, 178] and by De Salas & Amato,[170] prove that goitre in Argentina is definitely traceable to iodine deficiency in the waters, soils and foods of the affected districts. An iodine therapy campaign was launched in the northern provinces of Argentina in 1924 and again in 1938, control being exercised through physicians and teachers. Tablets containing 5 mg of iodine were distributed by the Public Health Service and iodized sweets were also used. Excellent results were obtained, but on the basis of this experience it was decided that if tablets are adopted as the prophylactic vehicle, it is preferable to issue them in 10-mg iodine strength. These may be given with safety even to quite small children. No cases of intolerance were encountered.

The Argentine Government is now tackling the goitre problem on a broader basis, and strong moves are being made towards the general introduction of iodized salt in all the seriously affected zones. Indeed, a law has already been passed making this practice compulsory in the Province of Mendoza.

Official concern is also reflected in the foundation of a Goitre Institute in the Faculty of Medicine at the University of Cuyo, Mendoza, under the direction of Dr H. Perinetti. Here, important field and laboratory studies of iodine-deficiency goitre have been carried out by Argentinian scientists, in collaboration with a team of experts from the famous Boston school of thyroidologists. The expedition, led by Dr J. B. Stanbury of the thyroid clinic of the Massachusetts General Hospital, demonstrated by means of radioactive iodine the great avidity of the thyroid of goitrous Argentinian patients for artificially administered iodine.[191-193] This uptake is related to the degree of iodine deficiency and is inversely proportional to the amount of iodine excreted in the urine. Attention was focused mainly on people below the age of 35 years, all of whom had goitres; usually these were diffuse, but a few were multinodular and of great size.

Goitre literature pertaining to Argentina is extensive. In addition to the sources already cited, papers by the following authors have been con-

Other interesting Chilean contributions to goitre knowledge are those by Covarrubias,[152] who writes on the relation between the thyroid gland and pregnancy, and by Cid Krebs [151] and Oberhauser Bund & Cid Krebs,[161] who have studied the iodine content of soils and waters in relation to goitre prevalence in the Province of Santiago

Argentina

Nowhere in the west of South America is goitre more widely diffused than in those provinces and territories of the Argentine Republic bordering the eastern slope of the Cordillera—namely (from north to south), Jujuy, Salta, Tucumán, Catamarca, La Rioja, San Juan, Mendoza, Neuquén, Rio Negro, and Chubut. In this great 1500-mile strip of territory goitre has been known since the Spanish conquest and it is of interest that one of the earliest and most impressive appeals for official intervention to deal with the menace relates to this area. Writing of Mendoza Province in 1820 Schmidtmeyer [169] says:

> The greatest number of the inhabitants of this state are afflicted with that unseemly and injurious disorder, the goitre, which prevails in so many parts of the world, and for the prevention of which little progress seems to have hitherto been made: yet the disease is such, as may justify an appeal to governments as well as to individuals, for farther and if possible more effectual efforts, for the discovery of its cause, and for the means gradually to remove it It cannot be supposed, that Providence should have destined so many countries of the earth permanently to produce this evil, and the numerous inhabitants compelled to reside in them, to be for ever subject to it: mental or bodily faculties are generally more or less affected by it, and those who have been in the vallies of Swisserland [sic] and Savoy know, how often they are lost by this severe visitation, which, however, can only be viewed as one of the very many imperfections which meet us at every step, and are intended to draw forth our labours and our exertions for their removal

Towards the centre of the country goitre is endemic in the Provinces of San Luis and Córdoba, and a very high prevalence is found in the Territory of Formosa and the Provinces of Corrientes and Misiones, all of which are eastern areas adjoining Paraguay, Brazil and/or Uruguay.

The precise rates in the various provinces and territories are not known; but some idea of the intensity may be gathered from surveys which have been carried out from time to time, particularly on schoolchildren. Thus, in some departments of Jujuy a goitre rate of 100% was observed by E. Sola (cited by De Salas & Amato [170]) in 1931. Later (1938), Lobo et al.[173] encountered 77 goitres in every 100 schoolchildren in the area of San Pedrito. Salta is no less goitrous. An examination of 1278 schoolchildren by Lewis [172] in 1924 revealed 87% in boys and 88% in girls. Lobo et al found from 15% to 45% in Salta schools examined in 1938, and Oñativia [180] has described goitrous cretinism in the Province as recently as 1959. In Tucumán rates of 65% in boys and 60% in girls have been recorded by Lewis, and the 1938 survey (Lobo et al.[173]) disclosed an average rate of

the east and north-east of the country, and in the Department of Colonia on the west side. In the capital, Montevideo, situated on the south coast of the country, goitre does not occur.[201, 202]

Thyroid enlargement accompanied by mental retardation among children in certain schools in the Department of Rivera (e g, at Sauzal) has obliged the local education authorities to prolong the period of a child's attendance at school.

There does not appear to be any absolute deficiency of iodine in the soils and waters of Uruguay. Likewise, the thyroid glands of human subjects, cattle and dogs, examined *post mortem*, show a normal iodine content. It seems, therefore, that the cause of goitre in Uruguay must be sought in some goitrogenic factor in food which is responsible for creating a relative deficiency of iodine.

Determinations of the calcium content of normal and pathological human thyroid glands by Pérez Fontana and his colleagues[203] showed that hyperthyroid glands had a low calcium content, whereas the calcium in hypothyroid glands was considerably augmented. There were insufficient data to establish a correlation between the amount of calcium in drinking-water and foods and the content of calcium in the thyroid

Brazil

Endemic goitre is a problem of exceptional gravity in parts of Brazil Pinotti[230] estimates that no less than 11 640 000 people in a total population of approximately 62 000 000 are affected The disease is particularly rampant in the southern States of Rio Grande, Santa Catarina, Paraná and São Paulo, the south-eastern States of Rio de Janeiro and Minas Gerais, and the great central and western States of Goiás and Mato Grosso In the north and north-eastern parts of the country, goitre is perhaps less noticeable; even so, the intensity in Maranhão and Piaui is considerable (11%) and there is a prevalence of around 9% in the vast territory of Amazonas and Rio Branco

Pinotti's[230] summary is given in Table V.

Goiás and Mato Grosso.

Towns especially affected with goitre in the interior of these states are Natividade, Conceicão, Arrayas, Goiás, Goiânia, and Cuiabá in the far west Silva & Borges[232] examined about half the children and young students regularly attending public and private educational establishments in the urban and rural zones of Cuiabá, Goiânia and Goiás—in all, 6803 persons of ages ranging from 7 to 21 years The prevalence was very high in all three zones, being 72% in Cuiabá, 66.6% in Goiânia and 81% in Goiás. The rates were higher among coloured than among white children, in girls than in boys, in the country than in the towns, in public than in private schools, and in lower than in upper economic groups.

sulted in preparing the foregoing summary: Bustos,[163] De La Barrera,[169] Maccarini,[174, 178] Olascoaga,[179] Perinetti,[183, 184] Romero,[187] and Schiavone.[188]

Paraguay

Goitre is extensive in the mountainous districts of Paraguay and has been a public health problem for many years. It is recorded by Burton [194] that at one time there was goitre in almost every home in Asunción. A reference in Schmidtmeyer's journal [189] suggests that the disease has been known in Paraguay at least since 1820.

Under the auspices of the Servicio Cooperativo Interamericano de Salud Pública, the present frequency of goitre in Paraguay has been determined from a study of recent hospital statistics and by the clinical examination of more than 44 000 children between the ages of 6 and 16 years in towns covering the most densely populated areas of the country.[195, 197, 198]

Peña [197] and Isasi Fleitas, [195] the two doctors chiefly responsible, found an average rate of 23.5% among children, the frequency in girls being four times that in boys. Children of families in comfortable circumstances were less affected than those from working-class homes. The hospital records show that the great majority of persons admitted for operative treatment were between the ages of 16 and 45 years.

In view of the prevalence of goitre more or less throughout the whole country, and the frequency of complications such as myxoedema and cretinism, iodized salt is officially recommended not only for children and pregnant women, but also for domestic animals in the endemic zone. During the three years 1946-48, tablets of Oridine, each containing 10 mg of iodine, were administered to children in four schools at the rate of one tablet per head weekly for about 20 weeks in each year. Before treatment the goitre rate was 26.1%, at the end of the first year's treatment it was 16.7%, by the end of the second year it had fallen to 8.2% and at the end of the third year it was down to 4.8%.[195]

Uruguay

A searching inquiry in 1935 led Pérez Fontana, Bennati & Volonterio [203] to conclude that goitre is not seriously endemic in Uruguay. Subsequent studies by Proto [204] and by Bauzá [199] and Bauzá, Cerviño & Salveraglio [200, 201] suggest, however, that certain areas are suspect and that the existence of a mildly goitrous zone must be acknowledged in the Departments of Salto, Tacuarembó and Rivera towards the north of the country. Among schoolchildren, Bauzá et al.[201] found visible goitres to the extent of 6% in Salto and 17% in Rivera; among older students, the proportion was 5.9% in Salto and 14% in Rivera.

Elsewhere, sporadic occurrences have been noted in various places: for example, in the Departments of Lavalleja, Rocha and Cerro Largo to

the east and north-east of the country, and in the Department of Colonia on the west side. In the capital, Montevideo, situated on the south coast of the country, goitre does not occur.[201, 202]

Thyroid enlargement accompanied by mental retardation among children in certain schools in the Department of Rivera (e g., at Sauzal) has obliged the local education authorities to prolong the period of a child's attendance at school

There does not appear to be any absolute deficiency of iodine in the soils and waters of Uruguay. Likewise, the thyroid glands of human subjects, cattle and dogs, examined *post mortem*, show a normal iodine content. It seems, therefore, that the cause of goitre in Uruguay must be sought in some goitrogenic factor in food which is responsible for creating a relative deficiency of iodine

Determinations of the calcium content of normal and pathological human thyroid glands by Pérez Fontana and his colleagues[203] showed that hyperthyroid glands had a low calcium content, whereas the calcium in hypothyroid glands was considerably augmented There were insufficient data to establish a correlation between the amount of calcium in drinking-water and foods and the content of calcium in the thyroid.

Brazil

Endemic goitre is a problem of exceptional gravity in parts of Brazil Pinotti[230] estimates that no less than 11 640 000 people in a total population of approximately 62 000 000 are affected The disease is particularly rampant in the southern States of Rio Grande, Santa Catarina, Paraná and São Paulo, the south-eastern States of Rio de Janeiro and Minas Gerais, and the great central and western States of Goiás and Mato Grosso In the north and north-eastern parts of the country, goitre is perhaps less noticeable, even so, the intensity in Maranhão and Piauí is considerable (11%) and there is a prevalence of around 9% in the vast territory of Amazonas and Rio Branco

Pinotti's[230] summary is given in Table V.

Goiás and Mato Grosso.

Towns especially affected with goitre in the interior of these states are Natividade, Conceição, Arrayas, Goias, Goiânia, and Cuiabá in the far west Silva & Borges[232] examined about half the children and young students regularly attending public and private educational establishments in the urban and rural zones of Cuiabá, Goiânia and Goiás—in all, 6803 persons of ages ranging from 7 to 21 years The prevalence was very high in all three zones, being 72% in Cuiabá, 66.6% in Goiânia and 81% in Goiás. The rates were higher among coloured than among white children, in girls than in boys, in the country than in the towns, in public than in private schools, and in lower than in upper economic groups.

TABLE V PREVALENCE OF GOITRE IN VARIOUS REGIONS OF BRAZIL

Region and population	Percentage with goitre	Total number affected
Central: 2 200 000		
Mato Grosso		
Goiás	53 8	1 150 000
South: 20 000 000		
São Paulo		
Paraná		
Santa Catarina	27 7	5 500 000
Rio Grande do Sul		
South-East: 16 000 000		
Minas Gerais		
Espírito Santo	27 0	4 300 000
Rio de Janeiro		
East: 6 500 000		
Sergipe		
Bahia	0 9	60 000
North: 2 300 000		
Amazonas		
Pará		
Rio Branco	9 4	210 000
Amapá		
Rondônia		
North-East: 15 100 000		
Maranhão		
Piauí	11 8	350 000
Ceará		
Rio Grande do Norte		
Paraíba	0 6	70 000
Pernambuco		
Alagoas		
Total: 62 100 000		11 640 000

São Paulo

An extensive study of endemic goitre among infants, schoolchildren and college students in different parts of the State of São Paulo has been made by Dr Arruda Sampaio.[205, 209] Between 1940 and 1947 he examined more than 22 000 individuals and found rates of from 5% to 10% in littoral

districts, gradually increasing as he passed up through the valley of the Parahiba river into the highlands of the interior, where rates of 60%, 70% and even 90% were encountered along the Serra da Mantiqueira, which dominates the hinterland between the towns of São Paulo and Rio de Janeiro.

Goitre here is of the simple type. Its prevalence increases with age in zones which have an average or low proportion, being about 20% higher in children between the ages of 12 and 15 years than in those between 8 and 10 years In heavily affected zones the goitre rate reaches a maximum even at pre-school age. Arruda Sampaio [209] mentions foci of endemic cretinism in the areas of his study and also refers to a case of almost total colour-blindness in a goitrous patient which successfully responded to iodine treatment.

Another considerable goitre centre in São Paulo lies 50 to 100 miles north-west of the capital and comprises the inland towns of Campinas, Botucatú, Pirambóia and Anhembi Here, a goitre inquiry has been made by Dr A. Lyra and Dr A. De Melo e Albuquerque [224] on behalf of the Diretoria do Serviço do Interior. They examined 850 boys and 712 girls from 5 schools in this region and found an average rate of 38.58% among boys and 44.80% among girls. In a later publication, De Melo e Albuquerque [216] refers to a rate of 70 6% among 3030 children examined by him at Campinas.

Paraná, Santa Catarina and Rio Grande do Sul

More than twenty years ago Duarte Nunes [218] reported that physical incapacity due to thyroid insufficiency was of frequent occurrence among army recruits examined by him in the military hospital at Curitiba Men with goitres were indolent, lazy and easily tired. After physical effort, tremor of the limbs was a marked feature. For these reasons Duarte Nunes recommended that anyone suffering from goitre be excluded from the Brazilian army

This matter has recently (1955) been re-examined in great detail by Paes de Oliveira et al [227, 228] Inspection of more than 120 000 young men of military age (19-20 years) drawn from nearly 200 municipalities in the States of Paraná, Santa Catarina and Rio Grande do Sul revealed that from 50% to 80% of recruits were rejected for service on account of ill-health and physical disability Among the causes of rejection goitre stands high, rates of 25% being common in the upland areas of southern Brazil

Minas Gerais

The goitrous districts of Minas Gerais lie from 100 to 200 miles due north of Rio de Janeiro at Barbacena, Ouro Prêto, Sabará, Congonhas and Conselheiro Lafaiete. The endemic presents a complex of symptoms

similar to that described *in other grossly affected areas—goitre, cretinism,* deaf-mutism and mental debility. Chemical examination of the local water-supply and vegetable foods clearly proves that the country is deficient in iodine. The antithyroid effects of the commonly used foods in Minas Gerais have been examined by Lopes [224]

Dr Lobo Leite,[220, 223] who is the recognized goitre authority in this area, found an average rate of 44% in the *town of Lafaiete (Queluz) and surrounding* rural districts With the co-operation of school officials he established a prophylactic centre for the purpose of distributing iodized chocolate to the schoolchildren twice a week A rate of 44% at the beginning of the scheme in 1940 had by 1942 declined to 27%. These two years of iodine prophylaxis also had the effect of greatly improving the mental alertness of the children. Many obtained higher marks and a larger number were promoted than before the iodine treatment was introduced. The preventive dose was ten times greater than the calculated need, but there were no harmful results.

Additional evidence of the goitre rate among the general population in Minas Gerais is provided by De Paula [217] and also by Pinto Viegas,[231] who found 252 records of thyroid disease among the case-sheets of 2500 miscellaneous patients in a doctor's private practice—a rate of 10%.

Rio de Janeiro

So great is the intensity of the endemic in the interior of the State of Rio de Janeiro that nearly all the inhabitants are affected and any person without goitre is regarded as abnormal. In 1944, out of every 1000 persons examined and treated by the Serviço de Endocrinología e Policlínica General, there were 387 with disorders of the thyroid gland (Peregrino [229]).

Amazonas and the North-East

So far as we have been able to ascertain, no records of endemic goitre in the Amazon area existed before 1956. About that time Lowenstein [225] became aware of the disease in the rubber-producing locality of Belterra, a community established by Henry Ford in 1934 south and slightly west of Santarém on a plateau overlooking the river Tapajoz, one of the largest southern tributaries of the Amazon river, it lies about 500 miles west of Belém. Here, in 1956, Lowenstein found dental caries and endemic goitre to be without doubt the main nutritional problems in a sample of 84 families (413 persons) he examined

One year later, Lowenstein made follow-up visits to 75 of his original 84 families to find that owing to higher wages granted in the interim, and consequently affording improved nutritional conditions, goitre rates had markedly regressed Nevertheless, a level of 10% to 20% is even now characteristic of this settlement.

Northern Europe

Iceland

Endemic goitre does not occur in any part of Iceland, nor has it ever been known to have occurred there; goitre in schoolchildren has never been detected and even sporadic cases of simple goitre are rare. But hyperthyroidism, including exophthalmic goitre, appears to be relatively frequent (Sigurjónsson [233, 235]). In short, whenever diffuse goitrous enlargement of the thyroid does occur in Iceland it is almost always accompanied by thyrotoxicosis Thus, of 50 diffuse goitres examined by Sigurjónsson, 38 were associated with Graves-Basedow disease, 10 were cases of simple hyperthyroidism, and only 2 were considered to be without definite symptoms of thyrotoxicosis

The absence of simple iodine-deficiency goitre in Iceland is undoubtedly due to the fact that the iodine intake of the population is high because of the large consumption of fish and fish products. This leads to an unusually high concentration of iodine in the thyroid and is the reason why in Iceland the human thyroid is exceptionally small

In the adult Icelandic male the average thyroid weight is about 14 g and in the female, 11 6 g. This is about half the accepted normal weight (25 g) of the non-goitrous thyroid in other countries. Correspondingly, the average iodine content per gram of dry substance is 4.01 mg in glands from males and 3 43 mg in those from females. This is double the average iodine content (2 mg per gram of dry substance) of normal glands from other non-goitrous countries It is clear, therefore, that the *total* amount of iodine in Icelandic thyroids is more or less the same as that found in normal thyroid glands elsewhere, namely, from 8 mg to 12 mg.

Finland

Wahlberg [256, 258] distinguishes four goitre belts in Finland, extending northwards from the coast of the Gulf of Finland into the central part of the country which has the most lakes The most easterly of these belts starts in the neighbourhood of Viipuri and continues north-eastwards around Lake Ladoga and across the Karelian Isthmus. Farther west, the second belt runs northwards from Miehikkala (St.-Michel) towards Jappilä. The third region lies immediately east of Lake Paijanne and the fourth west of it, Lake Paijanne thus intervening between these two goitrous areas There is a definite but not very severe endemic in Helsinki (Järvinen & Leikola [242, 243]) and a considerable number of cases occur on the Åland Islands (Lamberg et al [249]). Only the coast of the Gulf of Bothnia and the south-western part of the country lie outside the endemic zone.

On the basis of statistics obtained from the medical examination of military conscripts over a period of ten years, Wahlberg concludes that incidence depends on geological conditions The above-mentioned four

belts of high frequency are in that part of the country which was not submerged at the end of the Ice Age—areas which, compared with others, have a higher calcium and lower iodine content of soils and waters

The prevalence of goitre in Finland in relation to environmental iodine supply has been investigated by Adlercreutz,[236,237] by Virtanen & Virtanen,[253] by Vilkki,[254] and by Jarvinen & Leikola.[213] With the aid of radioactive iodine, Lamberg and his colleagues have carried out numerous metabolic and diagnostic studies in various endemic goitre areas of Finland [245 248, 260] Adlercreutz analysed a total of 74 samples of water from 60 different places in Finland and reached the conclusion that, generally speaking, there is a positive correlation between the occurrence of goitre and a low iodine content of water He found several exceptions, however, notably at Veteli, a town in the Department of Vaasa, where a water supply containing little iodine serves both a definite goitre area and its non-goitrous surroundings, and at Vartsila, where goitre is associated with a water of high iodine content Likewise, the observations of Lamberg et al. are consistent with the concept that endemic goitre in Finland is due chiefly to iodine deficiency, although contributory factors, such as naturally occurring goitrogens and hereditary and constitutional defects, are also operative. Jarvinen & Leikola touch upon the part played by abnormally high calcium and chlorine content of drinking water in the absence of sufficient iodine

The daily iodine intake from food and the urinary iodine excretion of men, women and girls from goitrous and non-goitrous rural areas have been compared by A I. Virtanen and E Virtanen, thus:

	Goitrous area			*Non-goitrous area*		
	men	*women*	*girls*	*men*	*women*	*girls*
Total iodine in daily diet (μg) .	53	56	52	68	62	70
Urinary iodine (μg per litre)	20 3	21 7	20 0	26 3	24 0	27 0

The recent study by Vilkki [254] deals with the iodine content of foods generally consumed in Finland and, in particular, with the iodine content of milk from two contrasted areas—namely, Turku, where the goitre rate is comparatively low, and Kuopio, where the rate is distinctly above the average for the country. Milk consumed in the Kuopio area, where goitre is prevalent, contains approximately 40% less iodine than milk from Turku, where the prevalence is low. The average iodine intake per person per day from all food sources is about 50 μg in the high-goitre area and about 70μg in the area of low prevalence Thus, the mean iodine supply in Finland is considerably below the minimum level of 100 μg per head per day recommended by the World Health Organization

On the question of the actual incidence of goitre in Finland, Wahlberg records that the endemic is responsible for 2000 operative cases annually out of a population of 3½ million. These account for 30 000 days of hospital attendance and give rise to numerous cases of chronic heart disease

For the purpose of assessing the goitre situation in Finland, 1000 consecutive parturients and their 1015 children (15 twin pregnancies) were examined by Hiilesmaa [239] in the First and Second Women's Clinics at the University of Helsinki Enlarged thyroids were found in 141 of these 1000 women; but if one includes the cases in which nodules (adenomata) were detected in non-enlarged thyroids, then the percentage of abnormal thyroids in this series of mothers rises from 14.1 to 28 4, as the following tabulation shows:

	Number of cases	*Number with nodules*	*Number without nodules*
With goitre . .	141	91	50
Without goitre .	859	143	716
Total examined	1000	234	766

Of 1015 infants born to these 1000 women, 139 were found to have goitre

The high proportion of cases with thyroid nodules is considered one of the chief characteristics of endemic goitre in Finland. Out of 952 cases of non-toxic simple goitre examined by Järvinen and Leikola [243] at Helsinki University Third Medical Clinic and in the medical wards of Kivelä Hospital no less than 483 (51 %) had one or more thyroid nodules, the smallest being pea-size.

Mortality from coronary disease among men is higher in Finland than in any other European country. Statistics suggest that cardiovascular symptoms are more prevalent in the eastern goitrous part of the country than in the western goitre-free areas. On post-mortem examination Uotila et al.[253] found that goitre was commoner, and the average weight of the thyroid higher, in 250 persons who died of coronary sclerosis than in 250 persons who died from other causes. They conclude that goitre and arteriosclerosis may have a pathogenic relationship, possibly through hypothyroidism and the overproduction of thyroid-stimulating hormone by the pituitary gland. According to Roine et al.[250] this parallelism between the geographical distribution of goitre and cardiovascular disease may be related to the significantly larger intake of iodine, ascorbic acid, and vitamin E in the non-goitrous west than in the goitrous east of the country.

Iodine deficiency in animals is frequently encountered in Finland R. Moberg (personal communication, 1949) says that the deficiency is so acute in the Karkkila district that saucers containing alcoholic tincture of iodine are customarily placed under the rafters of stables and cow-houses—a practice that is claimed to yield especially good results in overcoming reproductive failures Haaranen [235] has compared the thyroid weights of pigs from north-east Finland, where goitre is prevalent, with those from comparable animals reared in a non-endemic coastal area. The former were more than double the weight of the latter. Peltola & Vartiainen [249] were unable to prevent or alleviate thyroid enlargement in cattle from endemic areas and consider therefore that iodine deficiency in food is not the sole cause of goitre among animals in Finland

Goitre prevention throughout the whole of Finland by means of iodized salt is strongly advocated by Wahlberg, Uotila & Turpeinen;[259] but if this measure is not immediately practicable on such a large scale, it should certainly be applied at once in the most seriously affected areas—namely Tavastehus, Viipuri (Vyborg), St.-Michel and Kuopio. A comparison by Jussila [241] of goitre rates among schoolchildren showed that the frequency had fallen markedly between 1928/29 and 1953/54 in areas where the standard of living had risen and in communities reached by propaganda for iodine prophylaxis No change was seen in poorer districts with a low standard of living.

Sweden

According to Greenwald,[261] the first report of goitre in Sweden dates from 1815 and refers to its endemicity in and around Falun in Kopparberg. Today the disease has a fairly widespread distribution clearly defined by the exhaustive studies of Höjer.[262-266] From Vasternorrland and the northern and eastern parts of Jamtland the goitre belt extends southwards through practically the whole of Gavleborg and all Kopparberg, except the north-western tip, into Varmland, Västmanland and the northern part of Östergötland The southern goitre area extends from the Östergötland plain into the Counties of Jönköping, Kalmar and part of Kronoberg

Goitre-free or almost goitre-free areas are the plains of Skåne, Halland and Vastergotland, the district of Bohuslan and the plain of Dal, as well as the slopes of the tableland lying south-west of the city of Jönkoping The most northerly part of Norrland and the islands of Öland and Gotland in the Baltic are also goitre-free

Hojer and his survey team examined 29 000 people in 180 different places and found that, in the most severely goitrous areas, the goitre rate averages about 25%; but that there are many places where 15% of the population are affected They concluded that in all Sweden there must be not less than 300 000 people with goitre

An interesting feature of Hojer's investigation is the way in which he has been able to correlate goitre occurrence with the topographical lie of the land His fullest account [264] contains many explanatory sketches and diagrams showing the kind of terrain in which goitre is most likely to be found. Deep valleys with overhanging mountains, and areas at the foot of large slopes, are notorious goitre grounds Plains and high plateaux are less affected.

In so far as Norrland rivers are concerned, Hojer confirms McCarrison's thesis that goitre frequency gradually increases along a river valley as one passes from the source of the river to its mouth. These north Swedish rivers rise in goitre-free regions, pass through areas of sporadic occurrence and eventually flow into lands of considerable goitre intensity. In south Sweden, however, matters are quite the reverse. It is true that the Emån

river runs from end to end entirely through endemic goitre areas, but in the case of the Svartån and Stångån rivers, goitre is more prevalent in the upper reaches than in the lower. Similarly, rivers in the County of Blekinge, and those of Halland, flow from goitre areas into districts almost goitre-free.

According to Höjer's observations, wherever the prevalence of human goitre in Sweden is high, say, from 15% to 30%, one may almost certainly expect to find goitre among domestic animals—horses, cows, sheep, dogs, and cats. Where goitre is of sporadic occurrence, Höjer occasionally saw domestic animals affected, but in goitre-free districts he never found any goitrous animals

Toxic goitre is not unknown in Sweden. As might be expected, its distribution closely corresponds to that of simple endemic goitre (Sällström [267]). This is in accord with experience in many other countries. As regards cretinism, Höjer found about one case among every hundred persons in districts where goitre is endemic. A special study carried out in southern Sweden on the extent of mental deficiency in districts with varying degrees of goitre shows that mental deficiency increases with increasing prevalence of goitre.

The iodine content of milk from various districts in Sweden has been determined by Sjöström.[269] His results lend support to the iodine-deficiency theory of goitre causation. Sjöström [268] also determined the amount of iodine in water samples from sixty of Sweden's major water works; in this instance, however, he did not correlate the resultant data with goitre prevalence

Prevention of goitre by iodized salt is officially recommended in Sweden and instructions on how to obtain and use the salt have been circulated by the Royal Medical Department to all public health administrations and municipal medical officers

Norway

The most goitrous districts of Norway are found in a belt extending from the interior of Telemark County north-eastward for about 120 miles into Hedmark County where the country around Lake Mjosa is particularly affected Long recognized as goitrous, this zone was surveyed by Johannessen [272] in 1891 He tried to relate goitre occurrence with geological conformation and mentions strong endemicity in the country surrounding Tyrifjord, Randsfjord and Mjösafjord, and in such places as Lier, Modum, Ringerike and Toten

Kjlostad,[273] in a survey carried out in 1921, found a great deal of goitre among schoolchildren in towns in central Telemark In some places the rate was 80%, 90% or even 100% Typical percentages, for girls and boys respectively, were Bø, 45 and 55, Sanda, 74 and 96, Brunkeberg, 38 and 25, Flatdal, 55 and 44, Krokan, 29 and 80; Sandnes, 56 and 42; Utboen,

45 and 57 It is interesting that in several of these places the goitre rate was higher in boys than in girls; but the over-all figures for 537 girls and 510 boys in the Holla, Lunde, Bø, Seljord and Kviteseid areas were 57.5% in girls and 55 8% in boys.

Studies by Nicolaysen [278, 279] and by Lunde [274 276] refer to goitre among schoolchildren in towns bordering the Oslo Fjord and in the neighbouring area of Sandsvaer just south of Kongsberg. At Vittingfoss, for example, the rate was 55%, at Berg 38%, and at Komnes 40%. Considerably farther north, Nicolaysen found goitre in isolated districts throughout Gudbrandsdal in Opland and Österdal in Hedmark.

On the west coast of Norway cretinism occurs in the area immediately north of Bergen and south of the Sogn Fjord (Skaar [281]). North of the Sogn Fjord the prevalence in relation to environmental iodine supply has been studied by Iversen, Lunde & Wülfert.[271] At the isolated village of Veitestranden in Sogn 70% of the 500 inhabitants were found to be goitrous. Not far distant, the district of Vik in Sogn is goitre-free.

More recently, Devold & Closs [270] carried out a goitre survey in the district of Forsand near Stavanger. In this area goitre prevalence and thyroid size increased with distance from the sea, from 19.8% in men and 29 9% in women in the group nearest the sea to 35 9% in men and 62.8% in women in the group farthest up the valley. Noteworthy was the finding that consumption of fish by the people decreased as distance from the sea increased

Denmark

The older literature repeatedly states that Denmark is free from endemic goitre More recently, however, it has been shown that certain parts of the country have localized accumulations of goitre cases, not severe perhaps, but sufficiently noticeable to warrant medical attention and the need for preventive action Thus, in 1933 Dalsgaard-Nielsen [283] discovered a comparatively large number of goitres in Bedsted-Lø, a small parish in South Jutland lying between Aabenraa and Løgum Kloster. On more closely examining 40 unselected goitres in this area he found [284] that 23 were hyperthyroid, 6 were hypothyroid and 11 did not show any special characteristics.

The goitre problem in Denmark was subsequently elucidated more thoroughly in a comprehensive monograph by Rosenquist [288] who investigated the endemic area along the river Gudenaa between Silkeborg and Randers, particularly the district at Gern and Svostrup. He compared the prevalence at these places with that in the goitre-free district of Snejbjerg some 30 miles farther west. The percentage rates were as follows:

	Males	*Females*
Snejbjerg (goitre-free)	0 8	5 5
Gern (goitrous)	5 7	18 4
Svostrup (goitrous)	12 2	30 2

In the two goitre districts (Gern and Svestrup) a total of 2433 persons were examined of whom 363, or 14.9%, were goitrous. Forty-six, or 12.7%, of these 363 goitrous people showed symptoms suggestive of toxic goitre.

Meulengracht[257] and Iversen[243, 244] have shown that thyrotoxicosis increased noticeably in Denmark during the Second World War. Meulengracht's evidence, derived from records of hospital admissions, shows that a gradual rise in the number of cases of thyrotoxicosis during the period 1933–41 was followed by a sudden upward jump in 1942. The number of cases seen in his own clinic rose from 34 in 1941 to 118 in 1942. Meulengracht considered possible statistical fallacies in the returns, but concluded that both the steady rise between 1933 and 1941 and the abrupt increase in 1942 were real phenomena, though probably independent. He could not find any explanation for the rise; the 1942 "epidemic" could not be ascribed to the emotional disturbances of war, because in the histories of his patients he could find no abnormal occurrence of mental crises. Furthermore, there was apparently no corresponding increase in thyrotoxicosis in neighbouring countries involved in the war.

Iversen,[243, 244] who greatly amplified and extended Meulengracht's original observations and brought the matter up to 1947, confirms that the wartime increase in thyrotoxicosis in Denmark was a real one and not simply the result of better diagnosis. His figures relating to the city of Copenhagen are given in the tabulation below. They reveal a slow increase in incidence from 1938 to 1941, a sharp rise beginning in 1942 and reaching a peak in 1943–44, and a falling-off to 1947, when the rate was practically the same as in 1939–40.

Year	*Cases per 100 000 of population*
1938	19
1939	23
1940	23
1941	34
1942	77
1943	84
1944	83
1945	52
1946	31
1947	21

The psychological effects of the German occupation are not held responsible for the sudden change in prevalence because the behaviour of the invaders during 1941, when the rise in thyrotoxicosis began, was comparatively mild and there was no further rise in 1944, when conditions became much more exacting. Moreover, during the same period, the incidence and severity of toxic goitre tended to decrease in Belgium and the Netherlands, while in Norway a small increase in incidence during the early stages of the German occupation was followed by a fall.

Iversen points out that wartime changes in diet may have played some part and in this connexion puts forward the following interesting theory, although without proof Before the war large quantities of soya-bean-oil meal were imported into Denmark for feeding cattle. These imports were greatly reduced in 1940 and ceased entirely in 1941 and subsequent years. Soya bean is well known to contain an anti-thyroid factor which, when soya is normally used as cattle-feed, might find its way into cow's milk and thus supply the human population with sufficient anti-thyroid factor to keep down the incidence of thyrotoxicosis. If this were true, cases of thyrotoxicosis would tend to increase in number when, as in wartime, the supply of soya bean with its content of anti-thyroid factor was cut off

These speculations find some support from what in fact were the very opposite experiences of Belgium during the war Here, not only was there no increase in the absolute number of cases of toxic goitre, but the severity of existing cases appeared to decline Side by side with this was an increase in the incidence of simple goitre In explanation of these phenomena, Basteme,[282] who made the observations, points out that during the war the Belgian people tended to eat more and more vegetables of the *Brassica* genus—cabbage, kale and the like—which contain anti-thyroid substances. If the increased simple goitre in Belgium was in fact of the "cabbage" goitre type, then a reduction in severity might be expected in cases of toxic goitre on the same diet. The opposite effects might therefore be expected if anti-thyroid compounds were withdrawn from the diet. Such, it is postulated, was the case in Denmark during the war.

Estonian SSR, Latvian SSR and Lithuanian SSR

There does not appear to be much goitre in the former Baltic States Adelheim's data for Estonian schoolchildren are quoted by McClendon [296] and show a goitre rate of less than 0 5% in the four districts Hapsalu, Tallinn, Rakwere (Wesenberg) and Paide (Weissenstein). A later survey by Ucke [297] confirmed that there is little goitre in Estonia.

Goitre occurs in some districts of Latvia. Here, the special morphological characteristics of the disease have been described by Ilinskii.[289 291]

The iodine content of Latvian waters in relation to the distribution of goitre has been studied by Kupzis [293, 294] In general, where the disease is known to be absent or infrequent, as at Kemeri, Mitau, Silupe, Riga and the surrounding coastal districts, Liepaja in the west, and Wolmar in the north, waters contain between 2 μg and 15μg of iodine per litre. In contrast, iodine contents of 0.1 μg to 2 μg are found in areas farther inland where goitre is of common occurrence—namely, Zesvaine, Madona and Priekule.

Theses by Justus [292] and by Lewin,[295] published in 1913 and 1928 respectively, refer to the occurrence of goitre in Königsberg (Kaliningrad) and other neighbouring towns in Lithuania and what was formerly East Prussia,[a]

[a] Now part of Poland

notably at Memel (Klaipeda), Braunsberg (Braniewo), Lyck (Elk), Allenstein (Olsztyn), Neidenburg (Nidzica) and Osterode (Ostroda). Prevalence was mild, being about 5.78% in girls and 3.08% in boys. Modern data on goitre in this territory are lacking.

Netherlands

The first reliable goitre statistics from the Netherlands were those of Brand,[300] for whom the war of 1914-18 provided an opportunity to examine 46 975 mobilized servicemen from all parts of the country. He found that 10% of men from the Rhine-Maas area in the centre of the country had goitre, whereas only 1 4% of those from the Province of Groningen in the north were affected.

Subsequently (1924), the Central Board of Health of the Netherlands Government set up a special commission to study the goitre problem in greater detail and to advise on appropriate measures to remedy a situation which had apparently been getting gradually worse during the previous 25 years This commission—composed of clinical men, chemists, pathologists, bacteriologists and other experts—reported in 1932 on the examination of 34 000 children and adults in schools and factories.[301]

These new statistics for the most part confirmed Brand's distribution data of 15 years earlier and, as a result, a very detailed goitre map of the Netherlands has been made Broadly speaking, the eastern, central and southern parts of the country are prone to be goitrous, whereas the western and northern regions are almost free from the disease.

Immediately to the east of the Zuider Zee a considerable incidence has been found in such places as Wolvega, Steenwijk, Hoogeveen, Meppel and Kampen. At the south end of the Zee goitre occurs among the people of Harderwijk, Hilversum, Bussum, Naarden and Weesp Towards the eastern frontier the incidence is liable to be high in Emmen, Koevorden, Almelo, Enschede, Diepenheim, Boekelo, Winterswijk, Aalten and Doetinchem. Centrally, high figures were found among schoolchildren in the Betuwe ("river" area) at Tiel, Wamel and Leeuwen, and at Hoven, Arnhem, Ede, Renkum and, particularly, Kuilenburg, Gorinchem, the Krimpen area and Breda In the extreme south and south-east of the country the survey revealed goitre in Roermond, Eindhoven, Roosendaal and Bergen op Zoom, and on the western seaboard it has been found at Hillegom, Lisse, Sassenheim, Noordwijk and Warmond.

Places which are goitre-free, or have a negligible prevalence, are Assen and Groningen in the north, Zutphen in Gelderland, and Gouda and Barendrecht in the western part of the country In a recent nutrition survey of Ijsselmonde, goitre was encountered occasionally by Kaayk.[305]

An interesting study of goitre in the south-east corner of Friesland has been made by Pasma [306, 308] He refers particularly to the municipality of Ooststellingwerf, where 40% of the children were found to have thyroid

enlargement. In the same area goitre is common at Weststellingwerf and among very young children at Wolvega. Pasma observed that the intellectual level of the affected children was much below that of children who were goitre-free. Conditions in south-east Friesland are in marked contrast to those in north-west Friesland, which is entirely non-goitrous.

As part of the work of the Goitre Commission, Dr J. F. Reith, of the State Institute of Public Health at Utrecht, carried out a large number of analytical studies which prove conclusively that deficiency of iodine in the drinking-water is the cause of goitre in the Netherlands.[304, 309] The inverse relationship between the goitre rate and the iodine content of drinking-water is clearly seen in the tabulation below, which shows the percentage of goitre found among schoolchildren in various towns and the content of iodine in the water.[304]

	Goitre rate (%)	Iodine in water (µg per litre)		Goitre rate (%)	Iodine in water (µg per litre)
Hoogeveen	66	3.6	Harderwijk	45	2.3
Renkum	58	1.3	Doetinchem	44	2.4
Roosendaal	55	1.5	Kampen	41	0.9
Alemlo	53	3.0	Steenwijk	36	1.1
Gorinchem	52	3.0	Bergen op Zoom	31	1.1
Arnhem	50	1.0	Meppel	27	1.1
Kuilenburg	50	1.6	Zutphen	9	36.3
Ede	48	2.5	Gouda	6	69.8
Breda	47	1.7	Barendrecht	0	89.2

On the basis of their investigations the Goitre Commission reached the conclusion that, on an average, the daily intake of iodine from food and water was deficient by 80 µg per head of population. Accordingly they recommended that drinking-water in goitre regions should be fortified with potassium iodide so that each individual would receive approximately 80 µg of additional iodine per day. The *per caput* consumption of tap-water in prepared food and for drinking purposes was estimated to be 1.5 litres daily. It was therefore decided to raise the iodine content of tap-water by 50 µg per litre.

The iodizing installation used by the municipal water departments consisted of a glazed-stone mixing-vessel in which 100 litres of a 0.5% or 1% solution of potassium iodide were prepared. The addition of this stock solution to the main reservoir was achieved by means of a regulated dropping-needle, and the raised iodine content was checked by periodical analyses.

The Netherlands is the only country where goitre prophylaxis by iodized water has been successfully applied for any length of time on a large scale. In the hands of the Netherlands authorities the method has yielded results which compare favourably with those achieved in other countries by iodized salt. For example, at Kuilenburg a rate of 40% among children in 1931 had declined to 18% by 1937, to 14% by 1939 and to 4% by 1941.

Unhappily, plans to set up additional installations to supply iodine-rich tap-water throughout the country had to be abandoned on account of the 1939-45 war Indeed, the Germans stopped this form of prophylaxis entirely and it has never been re-introduced. As an alternative, the public health authorities advocated that all salt used for making bread be iodized in those municipalities which had previously applied the iodized-water method of prophylaxis. Accordingly, a decree came into force in 1942 making it compulsory for bakers in those particular municipalities to use only iodized salt—the so-called " Jobrozo ". Writing in 1952, De Josselin de Jong[301] states that Jobrozo (which contains 1 part of iodine in 33 000 parts of salt) is now used compulsorily for bread-making in 260 communities. Originally Jobrozo was somewhat more expensive than common salt; but the Royal Netherlands Salt Industry now produces it at the same cost. The results of this method of preventing goitre in the Netherlands have recently been described by Hipsley,[303] who has introduced the method in Australia

While officially controlled prophylaxis, first with iodized tap-water and later with bread salt, was gradually being applied town by town, a lively public awareness of the goitre problem became evident, and places not at once covered by the official measures began to introduce various uncontrolled prophylactic procedures of their own To regularize these independent activities the Royal Netherlands Salt Industry put on the market an iodized salt, called " Jozo ", for general use. This contains 1 part of potassium iodide in 200 000 parts of salt, and between 1932 and 1951 its production rose from 520 000 kg to 10 million kg

All the most up-to-date information on endemic goitre in the Netherlands, including the results of preventive measures, has been brought together recently (1959) in a comprehensive volume published by the Organization for Health Research under the authorship of Pasma, Terpstra, de Wijn, Kroes, & Langeveld.[302] The main conclusions from this remarkable survey deserve brief mention

Examination of large numbers of schoolchildren from all over the country shows that, apart from municipalities where iodine prophylaxis has brought about a decrease in goitre rates, only a few localities are goitre-free, namely, Zutphen, Gouda, Amersfoort, 's-Hertogenbosch, Barendrecht and Moordrecht It is stated that in these places absence of goitre is due to the fact that there is a sufficiently high iodine content in the tap water, the level being more than 40 μg per litre The remaining parts of the country still exhibit goitre in varying degrees of intensity. For instance, low rates are seen in the province of Zeeland; very high rates in the Gelderse Achterhoek.

Results of the Netherlands survey support the view that iodine deficiency is the primary cause of endemic goitre in the country Food is the most important natural source of iodine, drinking water ranks second, and, if the iodine content is high, may be the decisive prophylactic source of the

element. Proximity to the sea is of no practical consequence. In test subjects, thyroid uptake of radioactive iodine in an endemic area was avid and rapid.[310, 311]

Medical examination of children with and without goitre (but comparable in regard to age, sex and social class) revealed a better nutritional state in the goitre-free group; onset of puberty is on the whole a year later in goitrous than in non-goitrous children, systolic blood pressure is significantly lower in goitrous children, and in the intellectual and emotional sphere, goitrous children are at a disadvantage compared with their non-goitrous counterparts.

The Netherlands goitre campaign is a model of what can be done with determination and efficient management to rid a country of this disease. Within 20 years the youngest generation—children below 5 years of age—has been freed from the menace of goitre; serious cases are no longer observed among adults, the prevalence of moderate thyroid enlargement is decreasing steadily, and no harmful consequences of iodine prophylaxis have been reported (De Josselin de Jong [301]).

This account of goitre in the Netherlands would be incomplete without mention of the recent investigations of Binnerts,[298, 299] who, building upon the earlier studies of Brouwer and Wiertz, has clearly shown that as one passes from severely goitrous areas through mildly goitrous areas to regions where there is no goitre, there is a corresponding rise in the iodine content of the cow's milk collected.

Eastern Europe

Poland

Practically the whole of the south of Poland is goitrous. The disease occurs with high intensity in the Voivodship of Kraków, in Lower Silesia, and all along the northern slopes of the Carpathian Mountains westward into Sudetenland. In these parts the goitre rate is always about 10% and in some localities—notably in the Myślenice and Nowy Sacz districts of Kraków Voivodship—rises to 40% or even 60% (Hauke;[320] Samelson;[331] Chodzko & Tubiasz;[318] Tubiasz,[332 331] Nowakowski[330]). In 1953 Czyzewski et al [319] examined 6000 people in Lower Silesia and found pronounced thyroid enlargement in 17.8% of 3195 women and in 9.8% of 2805 men. *Król & Stylo [321] found 38% of cases among the 48 774 persons they examined* in the Voivodship of Kraków in 1957.

Goitre is also endemic in central and eastern Poland, in such places as Poznań, Zielona Góra, Krotoszyn, Leszno, Kalisz, Łódz, Warsaw, Kielce and Lublin. Here, the prevalence, although significant, is somewhat lower than in the south, being 13% in districts around Poznań and 21% to 28% at Krotoszyn (Czyżewski & Falkiewicz [315]). The disease is not endemic in the Voivodship of Białystok in the north-east of Poland where Karbowski [323]

examined 3421 men, women and children during 1953-1957. Nevertheless, Karbowski advises the application of iodine prophylaxis as a safety measure.

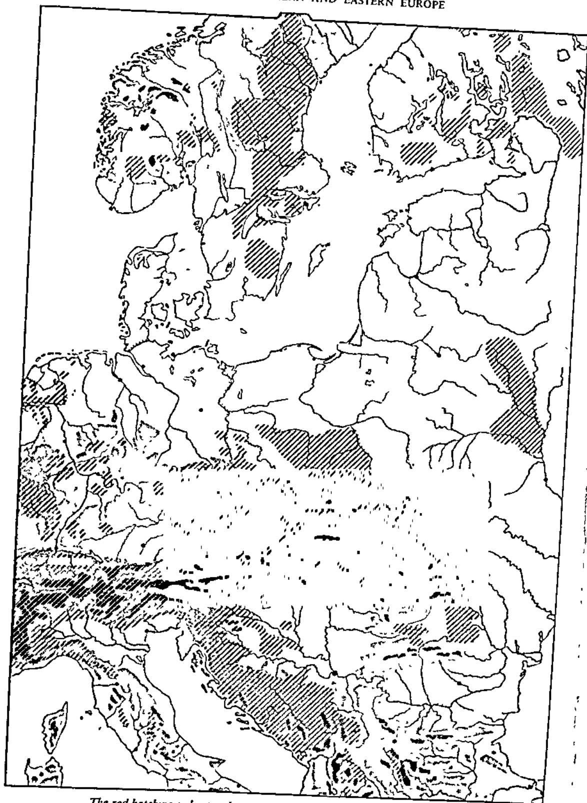
Surveys are now in progress at Gdańsk, Sopot and Gdynia on the Gulf of Danzig, and at Koszalin somewhat farther to the west, to ascertain whether goitre is of current public health significance in the northern section of Poland. Interest will centre on whether the findings confirm those of Liek[325-329] published between 1925 and 1929 that goitre does in fact occur in this area, albeit without great severity. Incidentally, Liek is one of those who reject the "iodine-lack" theory of causation.

Before the 1939-45 war a National Goitre Committee was established to collect statistical data and to apply prevention by iodized salt—a measure introduced in the Voivodship of Kraków on 1 January 1935. The results of this committee's work, available in papers by Tubiasz[331] and Heller,[321] show that an average rate of 17.6% of goitre among military recruits in Kraków Voivodship over the five years prior to salt iodization was reduced to 2% by 1938, that is, after three years of iodized-salt prophylaxis. This rapid and marked decrease in the goitre rate occurred with a salt iodized at a level of 1 in 200 000 and only in districts where the salt was employed. It was not observed elsewhere.

Post-war investigations have established that the distribution of goitre in Poland corresponds in general with that prevailing before the war, but the intensity of the disease has increased. The endemic is severest in the south, and individuals who have left goitre-free districts to come to live in Lower Silesia are known to develop goitre there. It appears, too, that a hitherto unknown endemic focus of considerable intensity exists in the region of Poznań. According to Heller,[322] the rise in goitre incidence in Central Europe (a similar increase has been found in Germany) was to be expected owing to quantitative and qualitative defects of diet during the war. He also attributes the rise to changes in fertilizer practice. In former times Chilean nitrate of soda, which contains a significant proportion of iodine, was extensively used in Poland; it has now been superseded by synthetic nitrogen fertilizers containing no iodine. Another contributory factor is said to be the cessation of kelp-burning for iodine on the coast of Brittany. Considerable volumes of iodine vapour from this source were carried inland by the prevailing winds, and Heller estimates that at one time about 14 tons of atmospheric iodine annually fell in rain on to Central European soils. The validity of this supposition is fully discussed in the *Geochemistry of Iodine*.[312]

The increased post-war severity of the disease has prompted the Ministry of Health to institute a preventive campaign on a national scale, and provincial goitre committees have been set up in Kraków, Lublin, Poznań, Warsaw, Katowice, Rzeszówa and Kielce, with the duty of mapping the extent of goitre in Poland and organizing the distribution of iodized salt.

FIG 3 NORTHERN AND EASTERN EUROPE



The red hatching indicates the areas where endemic goitre has been found

Iodized salt was re-instituted in the Voivodship of Kraków in 1946 and was introduced for the first time in that of Wroclaw in 1949

To make it possible for just comparisons to be made of results from different districts, the Ministry of Health have recommended the adoption throughout Poland of a uniform scale for measuring the degrees of goitre. A modification of the classification of Nowakowski is favoured—namely, group 1, in which the enlargement is less than half the size of the fist of the person examined; group 2, visible thyroid enlargement equal to half the size of the individual's fist; group 3, enlargement equal to the size of the individual's fist; group 4, enlargement greater than the size of the individual's fist.

A unique feature of the Polish preventive campaign is the proposal to transfer for a time all pregnant women and small children from endemic valleys to higher localities where goitre is non-existent This "settlement operation", as it is called, is based on experience in Switzerland, where as long ago as 1849 it was found that children transferred in this manner did not develop goitre to such an extent as those who had not changed their habitation

An evaluation of the iodine prophylactic programme in Lower Silesia has recently been made by Czyżewski et al [319]

USSR (excluding Estonian SSR, Latvian SSR and Lithuanian SSR)

In point of goitre distribution, the vast territories comprising the Union of Soviet Socialist Republics may conveniently be divided into three sections—European, Caucasian, and Asiatic

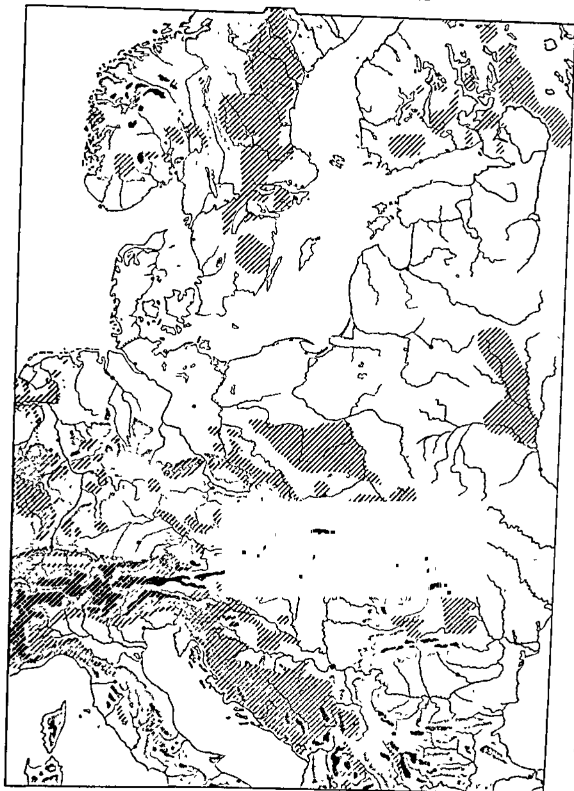
European section

In the European section eastwards as far as the Ural Mountains, which form the natural physical boundary of Europe, goitre occurs endemically in several places To the north-west numerous cases are found on the eastern shores of Lake Ladoga and in the area between Lake Ladoga and Lake Onega, particularly in the valley of the river Oyat and throughout the district of Olonetz. This focus may be regarded as an extension of the Finnish endemic

Byelorussia (White Russia) exhibits goitre in and around Minsk, and, farther south, in the marshy low-lying country drained by the Pripet and the Beresina rivers where about 20% of the schoolchildren are sufferers, but there is no cretinism The Ukraine has several goitrous localities, notably at Chernigov in the north-west and at Sumi, Kharkov and along the Tim river nearer the centre. South-eastwards from Kharkov there is goitre in the industrial district of Lisichansk-Rubezhansk.

The higher mountainous country towards western and south-western Ukraine bordering on Poland, Czechoslovakia and Romania is severely

FIG 3 NORTHERN AND EASTERN EUROPE



The red hatching indicates the areas where endemic goitre has been found

Batum itself there is an intense focus in the mountainous districts of Adzharistan.

In 1938, Gelovani [356] reported what was then a new endemic locality in Letshkhoom, an upland area of Georgia bordering on the lower part of Svanetia Here, 52% of the people suffer from goitre and there is much cretinism The water-supply of Letshkhoom villages is derived from shallow wells, to which the larger domestic animals also have access, and which have been proved by chemical analysis to contain little or no iodine.

In central Caucasia there is a goitre focus in the valley of the river Aragwa in Georgia north of Tiflis At the east end of the range in the vicinity of the Caspian Sea there are centres of goitre at Gunibsk and Laksk in Daghestan, and near Shemakha in the Republic of Azerbaidzhan west of Baku. Goitre occurs also in the extreme south of the Caucasian region, particularly at Ordubad where the provinces of Nakhichevan, Armenia and Azerbaidzhan adjoin The overall goitre rate at Ordubad in 1959 was 28.8% (Alikishibekov [338]).

Asiatic section

Eastward beyond the Caspian Sea, over the great Kara Kum desert and through Turkmen, there lie the Republics of Uzbek, Tadzhik and Kirghiz, which together encompass one of the most notorious goitre areas of the world In Tadzhikistan an inverse relationship has been found between the prevalence of goitre in certain districts and the amount of iodine present in local foods and water Experiments to control goitre by the iodization of bread have been undertaken in these localities

The central Asiatic endemic begins at Bukhara and Samarkand and reaches its greatest intensity in the Region of Ferghana (Kirghiz), especially in the Chatkal Mountains, around the towns of Tashkent, Kokand,[a] and Andizhan To the south of this area, abutting on the extreme north of Pakistan, lies the Pamir plateau, where in some valleys—notably that of the river Wanj which flows into the head-waters of the great river Oxus (Amu-Darya)—the entire population without exception is said to suffer from goitre The goitre endemic of Ferghana and the Pamir plateau is continuous with that extending south-eastwards through Kashmir and the Himalayas

Grouped with the Ferghana focus is the endemic found throughout the mountains of Semirechensk in " The Land of the Seven Rivers " between Lake Issyk-Kul in the north of Kirghiz and Lake Balkhash in Kazakh (formerly Turkestan) It was in this part of the world that Marco Polo saw goitres when on his famous travels from Venice to the court of the Grand Khan in China about the year 1275 After passing through the high Pamirs he came to the Chinese provinces of Kashgar and Yarkand at the

[a] Kokand has been described as " a city of cretins " (*Brit med J* 1905, I, 34)

goitrous in many parts. An extension of the Polish endemic is found at Lvov and in the Region of Volhynia, where the disease is reported to be mainly of the hyperthyroid and large colloid type, accompanied by considerable dental caries and severe disturbances of the circulatory and digestive systems.

Farther south, the Carpathian mountains carry the malady from Czechoslovakia and Romania into the West-Ukrainian areas of Stanislav Bukovina, Chernovitskaya, and northern Moldavia. Immediately to the south of Chernovitskaya there is a zone of high prevalence (56.5%) in the Vaškovskij district along the foothills of the Prut-Siret watershed. Here, the drinking waters contain an average of 0.55 μg of iodine per litre, whereas throughout the Kelmeneckij district in the neighbouring Prut-Dniester watershed to the east, the local drinking waters contain 2 15 μg of iodine per litre (Shvetz [416]) and, correspondingly, no goitre is seen

Another goitrous region in the European section of the USSR lies to the north-centre, relatively close to Moscow. The areas affected are to the north-east of Moscow at Yaroslavl, Kostroma and Ivanovo, and to the south at Serpukhov, Ryazan, and along the river Oka which drains part of the Central Russian Uplands

Proceeding eastwards towards the Ural Mountains one crosses a belt stretching from Kirov in the north to Saratov in the south. In the northern part of this belt, goitre is found on the Vyatka river near Kirov and in Mari Region between Gorki, Chuvash and Kazan The adjacent province of Tatar is also goitrous Farther down the Volga basin goitre occurs in the regions of Alatyr, Ulvanovsk, Penza, Kuznetsk, Syzra and the lower Volga town of Saratov The valley of the river Sok and the neighbouring area of Kuibyshev (Samara) east of Syzra are also reported to be goitrous.

In the main chain of the Urals goitre is found at various places, but particularly in the centre, on both the western and eastern slopes. The valley of the river Sylva and the nearby towns of Perm (Molotov), Debessy, Kungur, Krasnofimsk and Birsk are the chief seats of the disease on the western slopes. On the Siberian side, Sverdlovsk and Chelyabinsk are the principal goitre regions of the central Urals

Caucasian section

In the Caucasus, centres of goitre and cretinism are found all along the southern declivities of the mountains In the north-west, the valley of the Kuban river, which flows westward through the Territory of Krasnodar to enter the Black Sea just south of the Sea of Azov, is stated to have a goitre rate of 40% among the female population. High rates are also found in the adjoining areas of Karachaevsk and Kabardino-Balkarsk, especially around the Elbrus group of mountains.

In Gruzia (Georgia) the valleys of the rivers Ingur, Adzharis-Tskhali and Rion, which flow near Kutaisi into the eastern end of the Black Sea north of Batum, are well-known goitre areas, and in the neighbourhood of

elucidate whether incidence is related to excesses or deficiencies of mineral elements in the local soils, waters and foods. These clinical and geochemical surveys amply support the iodine-deficiency theory of causation, a conclusion with which all investigators, although maybe working in areas widely separated, are unanimously and uncompromisingly in agreement. As a consequence, organized preventive measures have been instituted under government auspices in almost every part of European and Asiatic Russia where goitre occurs.

One or two salient features of this All-Union effort deserve mention here:

Several investigators have been preoccupied with the environmental relationship between high manganese and low iodine. At the Kazan Medical Institute it has been found that in ordinary foods a high manganese and a low ascorbic acid content goes hand in hand with a high incidence of *endemic goitre*. Similar research in the adjacent Tatar Region has established that a high soil content of manganese occasions a reduced content of iodine in the soil, thereby leading to goitre occurrence (Kamchatnov[366, 367]). Gurevich[359, 360] reached the same conclusion from his studies in far-eastern Primorsk.

As regards absolute iodine content of soils, waters and foods, Shulpinov[415] found in Mari Region that dry soil in areas of high endemicity contained 122.2 μg, in areas of moderate endemicity 267.8 μg, and in areas free from goitre 1597 μg of iodine per 100 g. The iodine content of the potato in highly endemic areas was only one-thirtieth of that of potatoes grown in non-goitrous areas. Savchenko,[408, 409] who has made an "iodine map" of the Ukraine, found that the prevalence of endemic goitre was greatest when the iodine content of water did not exceed 1-2 μg per litre, moderate when water contained up to 2-3 μg per litre, and low when the level reached 3-4 μg per litre.

Results of iodine prophylactic measures are recorded by many observers. Bergman[345] testifies to their effectiveness in Transcarpathia. A re-survey of the Sverdlovsk region in the years 1957/59 revealed goitre rates one-fifth to one-third of those prevailing in 1929/31 when iodine prophylaxis was first introduced. After five years of systematic treatment with iodized salt (1952-1956/57) in the Stanislav area, goitre rates fell from 10.9% to 6.9% in the whole population, from 29% to 15% in expectant and nursing mothers, and from 17% to 11% among schoolchildren. The beneficial results of long-term iodine prophylactic programmes, extending over 25-30 years, have been documented by Nikolaev[400] for Russia as a whole, and by Mamedov and Orudzhiev[387] for the Caucasian republic of Azerbaidzhan.

In the all-embracing biogeochemical studies carried out in the USSR, animal goitre has not been forgotten. Few countries can boast a map more detailed and comprehensive than that prepared by Koval'skij[377] showing areas in which deficiency or excess of mineral elements in the soil may affect

extreme western end of the Takla Makan desert in Sinkiang (Chinese Turkestan) Writing of the people in Yarkand, Marco Polo [388] says: "They are in general afflicted with swellings in the legs, and tumours in the throat, occasioned by the quality of the water they drink" The leg swellings were due to elephantiasis

Elsewhere in the Asiatic section there are three major goitre areas These lie in the south of central Siberia, one at the head-waters of each of the three great parallel northward-flowing Siberian rivers—the Ob (or Obi), the Yenisei, and the Lena

Proceeding from west to east, the first of these three districts extends from the Altai Mountains, at the north-west corner of the Mongolian plateau, northwards to the town of Tomsk The endemic is especially severe in the middle and west Altai, that is, in Ojratsk, and covers the area of the sources of the rivers Ob, Bija, and Katun in the east Altai district of Kusnetz

The second focus lies in the upper basin of the Yenisei and centres round Tulunsk, a town on the trans-Siberian railroad midway between Krasnoyarsk and Irkutsk. The river Uda flows northwards through goitrous regions at this point Somewhat to the south-west of Krasnoyarsk the disease is rife in the Khakassia region where it has been a special problem among children and adults on the site of the Abakansk railroad construction Still farther east one encounters a considerable endemic around Lake Baikal and the head-waters of the river Lena. Here, in the neighbourhood of Irkutsk, about half the population are goitre sufferers In the middle reaches of the Lena a goitre belt stretches for more than 600 miles from Kirensk to Yakutsk.

East of Lake Baikal, in Buryat-Mongol and Chita (formerly Trans-Baikalia), goitre is found in two more or less circumscribed areas—one in the district watered by the river Chilok, which flows into the south-east end of Lake Baikal, and the other on the eastern slopes of the Yablonoi Mountains, particularly at the town of Nertchinsk and at the confluence of the Shilka and Argun with the Amur, rivers which form the boundary between this part of Soviet territory and the north of Manchuria Here, the goitre rate may reach 74% Arndt [310] records that goitre is often found in association with local endemics of osteo-arthritis Domestic animals are also affected with goitre in this area.

Finally, at the extreme east of the USSR goitre is found in the Primorsk Region, that strip of mountainous eastern seaboard territory extending from the mouth of the river Amur in the north to Vladivostok in the south

Goitre prevention throughout USSR

Throughout the whole of the Soviet Union an enormous amount of systematic and painstaking analytical and survey work has been carried out to establish the causes of goitre in different parts of the country and to

elucidate whether incidence is related to excesses or deficiencies of mineral elements in the local soils, waters and foods. These clinical and geochemical surveys amply support the iodine-deficiency theory of causation, a conclusion with which all investigators, although maybe working in areas widely separated, are unanimously and uncompromisingly in agreement As a consequence, organized preventive measures have been instituted under government auspices in almost every part of European and Asiatic Russia where goitre occurs

One or two salient features of this All-Union effort deserve mention here:

Several investigators have been preoccupied with the environmental relationship between high manganese and low iodine. At the Kazan Medical Institute it has been found that in ordinary foods a high manganese and a low ascorbic acid content goes hand in hand with a high incidence of endemic goitre. Similar research in the adjacent Tatar Region has established that a high soil content of manganese occasions a reduced content of iodine in the soil, thereby leading to goitre occurrence (Kamchatnov[366, 367]) Gurevich[358 360] reached the same conclusion from his studies in far-eastern Primorsk

As regards absolute iodine content of soils, waters and foods, Shulpinov[415] found in Mari Region that dry soil in areas of high endemicity contained 122.2 μg, in areas of moderate endemicity 267 8 μg, and in areas free from goitre 1597 μg of iodine per 100 g The iodine content of the potato in highly endemic areas was only one-thirtieth of that of potatoes grown in non-goitrous areas. Savchenko,[405, 409] who has made an " iodine map " of the Ukraine, found that the prevalence of endemic goitre was greatest when the iodine content of water did not exceed 1-2 μg per litre, moderate when water contained up to 2-3 μg per litre, and low when the level reached 3-4 μg per litre

Results of iodine prophylactic measures are recorded by many observers Bergman[345] testifies to their effectiveness in Transcarpathia A re-survey of the Sverdlovsk region in the years 1957/59 revealed goitre rates one-fifth to one-third of those prevailing in 1929/31 when iodine prophylaxis was first introduced After five years of systematic treatment with iodized salt (1952-1956/57) in the Stanislav area, goitre rates fell from 10 9% to 6.9% in the whole population, from 29% to 15% in expectant and nursing mothers, and from 17% to 11% among schoolchildren. The beneficial results of long-term iodine prophylactic programmes, extending over 25-30 years, have been documented by Nikolaev[400] for Russia as a whole, and by Mamedov and Orudzhiev[397] for the Caucasian republic of Azerbaidzhan

In the all-embracing biogeochemical studies carried out in the USSR, animal goitre has not been forgotten Few countries can boast a map more detailed and comprehensive than that prepared by Koval'skij[377] showing areas in which deficiency or excess of mineral elements in the soil may affect

human and animal health Soils of the non-chernozem zone of the Soviet Union are poor in copper, cobalt and iodine, a fact that influences the content of these microelements in fodder plants and therefore leads to animal diseases due to their deficiency.

The foregoing review of goitre distribution throughout the USSR is based on information taken from the comprehensive treatise on the subject by Arndt [340] and from papers by the following authors; localities with which particular authors are specially concerned are given within brackets

European section : Aber (Ukraine), [336] Antonov (Stanislav); [339] Bergman (Transcarpathia), [345] Chekalov (Kostroma and Ivanovo); [347] Davidova (Transcarpathia), [350] Fedinets (Transcarpathia), [353] Florinskii (Yaroslavl); [354, 355] Goncharov (Tatar & Mari); [357] Ionisyants (Smolensk); [362] Kamchatnov (Kazan), [365] Kamchatnov (Tatar & Mari); [366, 367] Karpova (Yaroslavl; [368, 369] Kharitonova (Sverdlovsk), [370, 371] Kutsherenko (Ukraine), [379, 380] Kutsherenko, Judina & Kutsherenko (Chernigov); [381] Kutsherenko, Judina & Rimak (Volhynia), [382] Landishev (Tim River), [384] *Lyapustin (Urals),* [385] *Mayer (Arctic),* [390] *Meshchenko (Transcarpathia);* [393, 394] Plotnikova (Sverdlovsk); [403] Primak (Ukraine); [404] Rodnjanski (Byelorussia), [405] Rybalkin (north Bukovina); [406] Savchenko (Ukraine), [408, 409] Schermann (Mari); [410] Shinkerman (Bukovina); [411, 412] Shmagina & Usmanova (Tatar), [414] Shulpinov (Mari); [415] Shvetz (Chernovitskaya); [416] Skatkov (Moscow district); [417 420] Tabakov (Birsk); [423] Tikhonova & Shifman (Lisichansk-Rubezhansk); [424] Tsarikovskaya et al. (Lisichansk-Rubezhansk); [425] Udod (Stanislav Region).[426]

Caucasian section Alfeev (Karachaevsk), [337] Alikishibekov (Ordubad), [338] Aslanishvili (Svanetia); [341] Balakhovskaya et al. (Daghestan), [342, 343] Egorov & Orudzhiev (Azerbaidzhan), [352] Ionisyants (Azerbaidzhan); [361] Kalishevskaya (Onskii, Georgia); [364] Kuznetsov (Karachaevsk); [383] Mamedov (Azerbaidzhan); [386] Mamedov & Orudzhiev (Azerbaidzhan), [387] Nikolaev (Kabardino-Balkarsk); [398] Nizhibitski (Karachaevsk), [401] Slavin (Kabardino-Balkarsk), [421] Strunnokov (Karachaevsk); [422] Valedinskaya (Kabardino-Balkarsk); [427] Zhukovski (Karachaevsk).[428]

Asiatic section : Abdulakhatov (Uzbek); [335] Belikhova (Abakansk); [344] Bolotova (Abakansk); [346] Chukanin & Levitin (Andizhan), [349] Gurevich (Primorsk), [358, 359] Gurevich & Mukhina (Primorsk), [360] Khazan (Tadzhikistan); [372] Khvorov & Ionisyants (Krasnoyarsk); [374] Kolomiitseva (Tadzhikistan); [375] Kruchinina (Uzbek); [378] Masumov (Ferghana); [389] Mirochnik (Khakassia); [396] Nikolaev (Khakassia), [399] Obliarov (Uzbek); [402] Shkarenko (Uzbek) [413]

Romania

The most highly goitrous regions of Romania lie along the Carpathian Mountains running from north to south of the country, and along the

Transylvanian Alps from west to east. Studies by Câmpeanu [431] and by Danielopolu and co-workers [432-437] contain a wealth of information, with numerous distribution maps and illustrations showing what must be among the saddest and most distressing cases of goitre and cretinism ever photographed

Two areas in which Danielopolu and his associates made a detailed investigation are Bukovina in the north (now part of the Ukraine) and the District of Sibiu, which lies in the centre of the country on the northern slopes of the Transylvanian Alps. In Bukovina, the Czeremosz valley, which traverses the Romanian-Ukrainian frontier, is highly goitrous, as also is the valley of the Moldavitza in the District of Câmpalung-Moldavia. Here, 46% of the inhabitants examined by Danielopolu had goitre. At Ispas in the Bukovinian district of Storojinet (now in the Ukraine) 465 cases were seen in seven small hamlets. Although simple goitre was commonest, there were many cases of cretinism, myxoedema, deaf-mutism and imbecility.

Among the communes investigated in the Transylvanian district of Sibiu were Tălmacuil with a goitre rate of 21.5%, Sibiel with a rate of 50%, and Cisnădie with a rate of 25.4%. At Ighisul-Nou, in the valley of the Târnava Mare immediately north of Sibiu, Danielopolu found 31.7% of goitre. Zlatna in the District of Alba Iulia to the north-west of Sibiu is also very goitrous

Goitre is prevalent in certain parts of Moldavia, on the east side of Romania Andronovici [429] examined the schoolchildren of thirteen Moldavian towns and found rates of 20 2% at Fălticeni, 24.1% at Jassy, 24 5% at Roman, 34 1% at Piatra Neamt and 13 5% at Bacău.

In Romania, goitre is notoriously a disease of poverty. The inhabitants of all the small goitrous villages surveyed by Danielopolu were very poor and lived under exceedingly primitive housing conditions—very often a whole family in one badly ventilated and ill-lit shack together with their domestic animals There is least goitre among the men who pass a large part of their time in the mountains as shepherds, woodmen and charcoal burners Social environment in relation to unfitness in military recruits in Romania during the years 1941-46 has been the subject of study by Banu & Dinu,[430] who mention goitre as one of the causes of rejection for service.

Romania now takes her place as one of the countries which has tackled the goitre problem with vision, determination and system. Prior to the year 1944 the State health authorities had done almost nothing to arrest the disease Shortly before that time attempts had been made to introduce iodized salt [a] and prophylactic dosage with Lugol's solution into some communities, but as these lacked official stimulus and supervision little came of them Not until 1947 did the Ministry of Health entrust to

---

[a] Parhon recommended its use in 1908 (*Rum med Rev*, 1, No 1, 61)

Dr S M Milcu the task of organizing an anti-goitre campaign throughout the country.

Under Milcu's direction, fresh surveys were undertaken by specially trained teams of endocrinologists, a goitre map of the country was built-up piece by piece, and preventive measures were set on foot To cover all the clinical forms and degrees of the goitre manifestation in Romania, Milcu introduced the term "endemic thyreopathic dystrophy", a three-degree classification into which all cases can be grouped according to severity. By a wider coverage of the country, and by uniform methods of examination, Milcu and his colleagues gave precision to earlier assessments of the extent and seriousness of the endemic Detailed surveys among schoolchildren belonging to communities in the Jiul valley to the south west, along the course of the Argeş river from Piteşti through Găeşti to Bucharest, in the Muscel region towards the centre of the country, and in the districts around Ploeşti and Slănic, revealed rates varying from 20% to 90%

Concurrently with these investigations, preventive action with iodized salt (1 in 50 000 strength) was instituted. An iodide tablet (1 mg KI) has also been used. Seven years of experience with these methods have been uniformly good The rate among schoolchildren has been cut by anything from one-fifth to one-third. Schools in the Muscel region, for example, showed a rate of 81 8% in 1950 and by 1954 this had been reduced to 46 5% as a result of iodine prophylaxis No more cases of cretinism or congenital goitre in children below the age of 4-5 years have been reported. Milcu and Negoescu [411] emphasize also that no accidents or ill-effects due to mass prophylaxis with iodized salt have been observed.

Full details of all the many-sided aspects of these recent Romanian studies are available in numerous papers and in several impressive volumes published under Milcu's editorship [438 418]

Bulgaria

Mass examination of 971 864 schoolchildren in 4 036 communities throughout Bulgaria showed that thirty-two provinces were affected with goitre in 1958, twelve severely The endemic regions are in the mountainous parts of the country, except for a few isolated foci, coastal areas are goitre-free (Penchev et al [439])

The disease is markedly prevalent along the banks and tributaries of the west Bulgarian river Struma, which rises in the Vitosha Planina south-west of Sofia and has a general north to south direction, eventually flowing through Greek Macedonia and entering the Aegean at the Gulf of Strimon on the east of Thessalonika In Greece the spelling of the name changes to Stroûma, and in classical times the river was known as Strymon.

The word "Struma" is often used, especially in German literature, as a synonym for goitre—the adjectives "scrofulous", "strumous" and

"goitrous" being nearly interchangeable. Some say that the river was named after the disease. It seems much more likely that the disease took the name of the river in whose valley it abounds.

Two left-bank tributaries of the Struma, the Rila and the Bistritsa, flow through exceptionally goitrous country where surveys have been made by a team under the leadership of Penchev,[455-458] and by Tsvetkov.[462] On the upper course of the Rila (which joins the Struma midway between Sofia and the northern border of Greece) 62% of a total of 3810 people examined in seven communities had goitres Newcomers into the area are not long in contracting the disease, and cretinism and deaf-mutism are of common occurrence On the lower course, a rate of 50 4% was recorded among more than 5000 people examined in the townships of Stob, Porominovo and Kocherinovo near the confluence of the Rila and Struma In these lower stretches of the river, cretins and deaf-mutes were not evident

More than 300 families (60% of all households) were examined for thyroid enlargement by Tsvetkov [462] in the township of Bistritsa situated on the river of the same name flowing through the extreme south of Sofia province into northern Macedonia Here, 47 3% of the inhabitants were found to be suffering from goitre

The city and district of Plovdiv towards the centre of the country is yet another goitre area in Bulgaria Khaidudov, Chervenivanov & Armenkov [452] associate the goitre endemic in this region with low nutritional standards and poor living conditions

The goitre rate among adults and schoolchildren in the town of Teteven, about 50 miles north-east of Sofia, was investigated by Ticholov [461] in 1926 and again in 1947. In the former year about 10% of the total population were affected; by 1947 this over-all figure had risen to 20%, and the rate among schoolchildren was as high as 80% In the village of Ribaritza, a strong focus of endemic goitre situated about 12 km from Teteven, no less than 81% of boys and 89% of girls were found to be goitrous in Ticholov's 1947 investigation Teteven was originally supplied with water from local springs and wells; in 1939 the source of supply was changed to water carried by aqueduct from the neighbouring river Beli-Vit. It has not been possible to determine the iodine content of both well and river supplies, but Ticholov *assumes that alteration in the chemical quality of the drinking-water is the cause of the increased incidence of goitre in Teteven.*

On the recommendation of Penchev,[459] Khaidudov [452] and others, steps are now being taken in Bulgaria to apply iodine preventive measures on a community scale

Yugoslavia

Endemic goitre is a serious public health problem in Yugoslavia, contributing much to chronic ill-health and lowered output; it adds signifi-

Dr S M Milcu the task of organizing an anti-goitre campaign throughout the country.

Under Milcu's direction, fresh surveys were undertaken by specially trained teams of endocrinologists, a goitre map of the country was built-up piece by piece, and preventive measures were set on foot. To cover all the clinical forms and degrees of the goitre manifestation in Romania, Milcu introduced the term "endemic thyreopathic dystrophy", a three-degree classification into which all cases can be grouped according to severity. By a wider coverage of the country, and by uniform methods of examination, Milcu and his colleagues gave precision to earlier assessments of the extent and seriousness of the endemic Detailed surveys among schoolchildren belonging to communities in the Jiul valley to the south west, along the course of the Argeş river from Piteşti through Găeşti to Bucharest, in the Muscel region towards the centre of the country, and in the districts around Ploeşti and Slănic, revealed rates varying from 20% to 90%.

Concurrently with these investigations, preventive action with iodized salt (1 in 50 000 strength) was instituted. An iodide tablet (1 mg KI) has also been used Seven years of experience with these methods have been uniformly good The rate among schoolchildren has been cut by anything from one-fifth to one-third Schools in the Muscel region, for example, showed a rate of 81.8% in 1950 and by 1954 this had been reduced to 46 5% as a result of iodine prophylaxis No more cases of cretinism or congenital goitre in children below the age of 4-5 years have been reported. Milcu and Negoescu [441] emphasize also that no accidents or ill-effects due to mass prophylaxis with iodized salt have been observed

Full details of all the many-sided aspects of these recent Romanian studies are available in numerous papers and in several impressive volumes published under Milcu's editorship [438, 418]

Bulgaria

Mass examination of 971 864 schoolchildren in 4 036 communities throughout Bulgaria showed that thirty-two provinces were affected with goitre in 1958, twelve severely The endemic regions are in the mountainous parts of the country, except for a few isolated foci, coastal areas are goitre-free (Penchev et al [439]).

The disease is markedly prevalent along the banks and tributaries of the west Bulgarian river Struma, which rises in the Vitosha Planina south-west of Sofia and has a general north to south direction, eventually flowing through Greek Macedonia and entering the Aegean at the Gulf of Strimon on the east of Thessalonika In Greece the spelling of the name changes to Stroûma, and in classical times the river was known as Strymon.

The word "Struma" is often used, especially in German literature, as a synonym for goitre—the adjectives "scrofulous", "strumous" and

confirmed the well-known finding of many earlier investigators that goitre develops more readily in rapidly growing children—the tall, heavy, rather dull pupils at school The physiological demand for thyroid hormone is less in smaller, lighter children, among whom thyroid enlargement is consequently less evident.

Extending their studies from the Croatian mainland to the adjacent Adriatic islands, Ferber & Buzina (quoted by Horvat & Maver [473]) noticed a high incidence (40%-46%) of goitre on the island of Krk, whereas on other neighbouring islands the disease is very rare or wholly absent. On closer investigation of this interesting phenomenon, Horvat & Maver [473] reached the conclusion that goitre in Krk is the result of a complex nutritional deficiency involving not only lack of iodine but also deficiency of vitamin A. Subsequent studies with ^{131}I do not, however, entirely support this suggestion; it seems that a low iodine intake, aggravated no doubt by factors impairing iodine utilization, is the dominant goitre-producing agency (Buzina et al ;[468] Horvat et al [471]).

Bosnia and Herzegovina

Although endemic goitre in Bosnia and Herzegovina has been a subject of intermittent study for more than 80 years—indeed, since Austrian replaced Turkish rule in 1878—exact information did not become available until the modern surveys of Žarković & Radovanović [494] conducted under official auspices In 1953 the Yugoslav Commission for Medical Scientific Research sponsored a study in the district of Srebrenica north-east of Sarajevo and found 75% of all schoolchildren had manifest goitre.[478, 494] Three years later (1956), an organized mass examination of 34 343 persons of all age-groups over six years drawn from 975 settlements spread throughout the entire Republic of Bosnia and Herzegovina (approximately 1% of the total population) exposed an average goitre rate of 20% among males and 33% among females The districts of Brčko, Sarajevo, Goražde, Fojnica and Trebinje in the eastern section of the country, and Banja Luka in the north, are hyperendemic regions Contrary to earlier assumptions, the Sava river valley in the north was found to be as strongly goitrous as the Drina valley in the south

No positive correlation was established between the amount of iodine in drinking water and the prevalence of goitre in Bosnia and Herzegovina, but this, as Žarković and Radovanović [494] say:

. cannot be taken as proof that lack of iodine is not the most important single agent in the epidemiology of goitre First of all, the analysis of one sample of water—let alone a sample taken at the time of the lowest water-level in sources and wells— cannot be considered representative of the annual content of iodine and still less of the iodine content in a decade Besides, water is not the only source of iodine for the population Big differences in the types of food and in their iodine content are characteristic of Bosnia and Herzegovina, and certain foods might compensate for or aggravate the lack of iodine in the water Finally, the differences in goitre prevalence among people with equal con-

cantly to the cost of State medical care. The general distribution of the disease has been described by Simitch,[493] by Miholić,[482] by Ramzin, Bučić & Lukić,[490] and by Matovinović; [480] detailed surveys of particular areas have been made by numerous other workers whose findings are noted below, the occurrence of thyroid enlargement in domestic animals is discussed by Jovanović, Pantić & Marković,[475, 476, 483] and the problem of goitre in the army has been the concern of Ceramilac.[469]

The goitrous area extends continuously for more than 500 miles from Slovenia in the north-west to the extreme south-western corner of the country in the neighbourhood of Bitolj (Monastir) and the lakes Presba and Okrida in Macedonia The only goitre-free areas lie along the Adriatic coast and throughout Vojvodina in the north-east. The intensity of the endemic varies. It is highest on the banks of the river Ibar and in certain valleys of the Zlatar Planina in the *sandjak* of Novi Pazar, i e, in the south-western part of Serbia Slovenia, too, has high rates; and severity is considerable in Croatia, in Bosnia and Herzegovina, and in northern Montenegro Goitre in Yugoslavia is mostly located in high mountain districts and tablelands, but is also found in river valleys and in the plains.

Slovenia

In the north-west of the country (Slovenia) there is considerable goitre throughout the head-waters of the rivers Sava and Drava (Danube) between the towns of Ljubljana and Maribor (Marburg) This centre, which is an extension of the Klagenfurt-Graz goitre area in southern Austria, has been specially studied by Arko,[465] who mentions the following places as goitrous: the mountains of Kozjak, Pohorje and Haloze, and the low-lying area of the Pannonian plain in the vicinity of Beltinci. Arko very carefully examined 257 children (up to 14 years of age) in the village of Zetale near Rogašk Statina and found goitre in 60% of them

Croatia

An investigation of the Croatian villages of Rude and Braslovje, in the near vicinity of Zagreb, undertaken jointly by the Institute of Hygiene and the Clinic of Internal Medicine, Zagreb, showed thyroid enlargement in 83 3% of 856 persons examined. More than 58% of these cases had severe goitres of the first degree, and 10% of the total population of the two villages were handicapped for hard physical work on that account Twenty cretins were found among the 856 people examined (Ferber et al.; [470] Matovinović [480]). Buzina et al [467] say that in Croatia goitre is most widespread in the district of Jastrebarsko south-west of Zagreb and in Virovitica situated due east of the capital almost on the Hungarian border.

Prebeg et al.[486] examined 21 482 Zagreb schoolchildren in 1953/54 prior to the compulsory iodization of salt and found an overall goitre rate of 46 5%, the proportion being 42.2% in boys and 50 9% in girls. They

dwarfism, sterility or low vitality In sheep, the thyroid enlargement was not so pronounced but poor lactation, poor wool production, and a high mortality rate among lambs were noteworthy. Sterility, low milk yield, short lactation, too frequent silent heat, and poor condition of young stock are the symptoms of hypothyroidism reported in cattle Little abnormality was seen in pigs. Horses also suffer from goitre, the incidence being higher in primitive than in important breeds. Affected animals were less able to work, and stallions had decreased sexual impulse. Foals do not develop normally and are often stunted

Owing to the seriousness of the goitre endemic in Yugoslavia, the Government is giving every support to control programmes, and, in keeping with recommendations made by the World Health Organization, has passed a law, effective from 1 July 1954, requiring the iodization of salt at a level of 10 mg of potassium iodide per kg of salt. Salt-iodization plant has been installed on a pilot scale and will be increased until all salt distributed for human consumption is iodized in conformity with this regulation (Matovinović;[480] Brožek & Ferber[466])

Albania

In Albania thyroid disease is known at Berat towards the south of the country There is no published literature on goitre in Albania; the foregoing information was communicated privately by C Evelpidi (1948)

Greece

Reports communicated privately by Evelpidi (1948) of goitre in and around Poroy, Djuma and Sérrai (three towns situated on the edge of the lowland Grecian slopes where the Struma valley broadens into the plains of Greek Macedonia) and also farther west at Karadjova in the Yiannitza-Vodená area, have been confirmed by Hadjidakis[495] His field enquiry, part of a State programme to improve Mother & Child Welfare, involving the clinical examination of almost 12 000 children and youths, disclosed a goitre rate of 53% in an appreciable number of villages in the northern districts of Greece, especially in Thessalonika, Macedonia, and Epirus Although iodine deficiency could not be chemically proved, the fact that in some instances goitre prevalence diminished following iodine administration indicated the probable influence of this agency

Central and Southern Europe

Austria

Goitre has long been a concern of Austrian preventive medicine Prophylactic admixture of potassium iodide with common rock salt in the proportion of 1 part of iodide in 10 000 parts of salt was strongly recom-

sumption of iodine might be produced by a series of other influences, including differing doses of various goitrogenic factors.

Serbia and Montenegro

Much has been written about the severe south Serbian focus, which includes the valleys of the Lim, Uvac, and other rivers flowing from the Zlatar Planina, the towns of Nova Varos, Prijepolje, and Novi Pazar, and extends eastwards over the river Ibar to the Kopaonik and Jastrebac Mountains in Moravia, with a southwards branch into the Kosovo-Polje plains and the valley of the river Vardar at Skoplje Simić et al.[492] found a rate of 6% to 12% in 147 families (758 individuals) in three villages of the Šumadija region. Gvozdenović[472] records a morbidity varying from 37.8% to 60 7% among the people of Mataruge in the Kraljevo district of central Serbia, and in the village of Gornia Jošanica in the Jastrebac mountains, Kičić & Radmili[478] diagnosed nodular goitre in no less than 366 (57.6%) out of 759 persons examined Olive Lodge[479] in her book *Peasant Life in Yugoslavia* writes that 80% to 85% of the population of the *sandjak* suffer from enlarged thyroids

The detailed survey made by Schneider & Ganss[491] in the villages and valleys surrounding the Zlatar Planina offers good examples of the variations in prevalence which may occur within a comparatively small area. At Hisardžik, a small mountain village of 250 people situated on the southern slope of the deep valley of the river Miloševo, 60 out of 80 persons examined had pathologically enlarged thyroids Further up the same valley, at Karaula, there was no goitre at all; nor could any cases be found at Kačevo, a settlement close to Hisardžik. Similarly, in the not-far-distant Kosatica valley the upper reaches are goitre-free while the lower part is distinctly goitrous. High up on the top of the Zlatar Plateau itself, goitre is completely unknown, but in the northern declivities at Nova Varos and lower down the Bistrica valley " lovely " goitres are seen.

Schneider & Ganss[491] attribute these variations to sharp distinctions in local geology and topography. Goitre occurs only in valleys, not on plateaux. Valleys in which the slopes are chiefly covered with soft rich soils are not goitrous; those with steep wall-like sides scantily covered with poor soil favour the disease. The incidence is higher where faults and folds predominate, and at the intersection of strata of different ages.

In northern Montenegro goitre is prevalent throughout the upper basin of the river Lim, particularly in the neighbourhood of Bijelo Polje, and cretinism is of frequent occurrence (Gušić et al.[471]). Macedonia at the extreme south of Yugoslavia is another region of high prevalence, especially in mountain areas where chestnut trees abound (Petrov[485]).

Jovanović, Pantić & Marković[475, 476, 483] describe hypothyroidism occurring among domestic animals in areas where the human population suffers from goitre. Goats showed most thyroid enlargement but no signs of

for instance, the rate for children is 49%. The fact that 11% of Bad Hall children have goitre in spite of a high iodine intake from water is evidence that iodine deficiency is not the whole etiological explanation; goitrogens in food, bad hygiene, or other factors may also be involved (Kopf[502]).

Studies of the occurrence of endemic goitre among people who have moved from goitre-free areas into affected areas have been made by Schreckels.[508] He examined 2220 such people in and around Salzburg and found that within a year of coming to live in the goitre area 40% of them developed thyroid enlargement. The longer the people had been settled in the area, the higher was the prevalence of goitre among them.

A feature of the goitre endemic in Austria stressed by Kriebernig[501] is the increase in prevalence which has taken place in post-war years, especially in the newborn. This happened both after the First World War (Abels[496]) and after the Second. Sollgruber[510] gives the following figures: among 4800 newborn infants examined in the ten years 1944-53 in the maternity ward of Dornbirn hospital in Vorarlberg, the average goitre rate was 7%; in the two years 1952 and 1953 the rate was 11% and in the first quarter of 1954, 20%. Sollgruber treats these infants from the third day of life with large doses of iodine spread over several days. He strongly recommends the general use of iodized salt and considers it should be the standard salt on sale everywhere, untreated salt being obtainable only on special prescription. Kopf[502] records that, in Vöcklabruck, administration of potassium iodide to pregnant women, preferably from the fourth month, reduced the goitre rate in the newborn from 47% to about 5% in the space of two years.

Hungary

According to Kiss,[520] there are 500 000 goitrous people in Hungary. Endemic cretinism is said to have been known in the country since the 14th and 15th centuries.[511] Broadly speaking, goitre is confined to three main parts of Hungary—the northern frontier, the west-centre and south-west, and the neighbourhood of Debrecen in the north-east. The Great Hungarian Plain in the centre and east of the country is goitre-free.

Upper Hungarian localities affected are: Magyaróvár, on the river Leitha in the extreme north-west, where a percentage prevalence in school-children of 33.3 has been recorded; Komárom, with a rate of 35%; and Tatabánya, with a rate of 59.3% among children. Farther east, children in the northern towns of Vac, Salgótarján and Miskolc in Upper Hungary showed rates of 9.3%, 17.5% and 14.5%, respectively. In the department of Nógrád due north of Budapest on the Slovakian border, Kiss[520] examined

mended by Köstl[503] in 1855, more than 100 years ago. With the exception of a few districts in the Danube valley and in the direction of the Hungarian plain to the east, practically the whole country is goitrous. From west to east the most notorious localities are:

(1) The Province of Vorarlberg, which is bounded by the Swiss Alps, Lake Constance and the Algauer Alps to the south of Bavaria. Here, the district of Montafon south of Bludenz is specially affected

(2) The Tirol, especially in the neighbourhood of Telfs and Innsbruck.

(3) The Province of Salzburg, particularly along the river Salzach at Zell-am-See and Taxenbach. The city of Salzburg itself has a high goitre rate

(4) The Province of Kärnten (Carinthia), especially the area around Klagenfurt This includes the valley of the river Drau (Drava) and the towns of Friesach, Wolfsberg and St Paul

(5) The Province of Steiermark (Styria) where the areas around Murau and Judenburg have a high incidence. The town of Graz on the eastern edge of the Styrian Mountains and many other places along the valley of the river Mur are mildly goitrous.

(6) Upper Austria in the vicinity of Vocklabruck, Bad Hall, Steyr, and Rohrbach north-west of Linz

(7) The extreme east of the country is the least affected. Nevertheless, many cases are found in Burgenland Province on the borders of Hungary, and in Vienna, the capital city (Schroetter,[509] Burtscher & Sprenger;[499] Wagner-Jauregg,[511, 512] Bauhofer,[497] Kopf;[501] Kutschera-Aichbergen[505]).

The prevalence throughout Austria is high. Taking the country as a whole, 44.2% of boys and 48 1% of girls were found to be goitrous in the 1923-24 survey of 686 000 schoolchildren organized by Wagner-Jauregg.[511, 512] The highest regional rates were in Vorarlberg Province, with percentages of 58 9 in boys and 63.6 in girls The lowest rates were in Burgenland Province, with 15 9% in boys and 19.5% in girls. The city of Vienna showed percentages of 41 1 in boys and 46 2 in girls.

The situation in more recent times is scarcely less acute. A survey of five groups of Viennese civilians under United States occupation in 1945 revealed non-toxic diffuse goitre in from 21% to 42% of those examined, the rate in children under 14 years being 38% in boys and 35% in girls (Davidson et al.[500]) In the Upper Austrian town of Rohrbach, notorious for its high goitre rate, the percentage with thyroid enlargement was 31 in 1952 compared with 66 in 1946. The drop is due to the adoption of iodine preventive treatment. At Bad Hall, an Upper Austrian watering-place well known for the high iodine content of its drinking-water, about 11% of schoolchildren are affected. In contrast, the rate among children living outside the town in nearby districts is 35% or even higher. In Steyr,

from goitre is found where the water contains more than 25 μg of iodine per litre. If the iodine value is between 13.5 μg and 25 μg per litre, protection against the disease depends on the hardness, while for values between 5 μg and 13 5 μg per litre freedom from goitre is ascribed, irrespective of the hardness of the water, to a high content of iodine in the soil. Where the water contains less than 3 μg of iodine per litre, goitre appears whether the water is hard or not.

Iodized salt (10 mg of KI per 1000 g of salt) was officially introduced into certain parts of Hungary in 1948, and the results of five years' prophylaxis by this means have been summarized by Sós & Szabó.[526] The most marked improvement has occurred in the west and north of the country, particularly among children. No very significant reduction in prevalence has been noticed in the south trans-Danubian region.

Czechoslovakia

Maps prepared by Feix, Rezler & Šilink,[539, 540] on the basis of the examination of 44 262 men and women and 85 060 children from all districts of Bohemia and Moravia in 1947-48, show that thyroid enlargement of every type is prevalent to a considerable degree throughout the whole of these regions of Czechoslovakia In some communities the frequency may be as high as 100% among women

Data on the distribution of goitre in army recruits collected by Klíma [541] in 1933 reveal a marked focus along the Erzgebirge on the Saxony border to the west of Bohemia, especially in the neighbourhood of Karlovy Vary (Karlsbad) and Pilsen. This western belt extends round the northern Sudetenland frontier, through such places as Usti and Liberec, and links up with the Silesian goitre districts of south-west Poland

Determinations of the urinary output of iodine by individuals in 29 west Bohemian communities situated in the neighbourhood of Liberec, Usti, Prague, Pilsen and Karlsbad have been made by Vohnout & Pihar [570] On the assumption that the minimum iodine requirement is 100 μg per head daily, the results show that people in these regions have an intake of iodine deficient by 30-80 μg per day.

During the years 1949 to 1954, Hostomská et al [543] treated 1931 Prague children in age-groups from 3 to 15 years with thyroglobulin plus iodized salt in strengths of 1 in 100 000 to 1 in 40 000 A considerable decrease in the size of both medium and small goitres resulted. In the Prague area, goitre is also reported from the towns of Dobříš, Roudnice and Sušice (Fleischhans,[511] Šilink & Maršiková [560]) In Sušice and neighbourhood, all schoolchildren and most workers in the Union of Agricultural Co-operatives were examined by Horáčková & Pokorný,[542] who found hyperthyroidism to be the most common type of thyroid disturbance even where cretinism is traditional. The intensity of the endemic in this district has

tyán community could offer only two cases among 1800 inhabitants. Here, the local water, known as "Iodaqua", is regarded as "medicinal" and contains among other therapeutic ingredients a high proportion of iodine. Besides being goitre-preventive, "Iodaqua" is reputed to have significantly beneficial effects on general health, especially in reducing abnormally high blood pressure. In Budapest and surrounding districts, from 5% to 12% of children are said to be goitrous (Gortvay;[515] Bodnár & Straub;[513] Straub;[529, 530] Sós, Fekete & Molnár[525])

In the west-central part of the country near Lake Balaton, children in the towns of Sümeg and Tapolca showed rates of 11% and 10.1%, respectively; but at Tihany, which lies immediately on the lake shore, there is no goitre (Straub[528]). According to Véli,[537] schoolchildren are considerably affected in the town of Kaposvár, which lies between Lake Balaton and Pécs. In this general area, too, a goitre endemic among the children of Komló has been reported by Várbiró, Száva & Koch.[536] In Pécs itself, thyroid enlargement is commonly seen in newborn infants, among schoolchildren (who exhibit a rate of 10% to 13%) and in older people (Hal & Horváth,[516] Horváth and co-workers[518, 519]). The iodine content of food and water in relation to goitre in Pécs was determined in 1933 by Scheffer[522] and again in 1949 by Horváth, Nógrádi & Dános.[518] The latter study showed that one part of the city supply contained 4.5 µg of iodine per litre and another part 1.5-2.0 µg per litre. Goitre was commoner in that part of the city supplied exclusively with water of the lower iodine content.

In the extreme east of Hungary, little goitre is seen, but there are exceptions—notably in the neighbourhood of Debrecen, where the following goitre rates have been recorded by Straub & Török:[533] Hajduhadház (11.7%), Vamospércs (22.6%), Újhuta (40%-50%), Óhuta (50%-60%), Budahegyközség (82.2%) and Ómassa (83.3%). In 1947, Kiss[521] drew attention to the increasing prevalence of goitre in Nádudvár, in the Debrecen area.

A feature of the goitre literature of Hungary is the several attempts that have been made to find out whether the radioactivity of soils and their fluorine content are factors implicated in the causation of goitre. Straub & Kovács[532] conclude from their investigations that goitre will not develop from the consumption of fluorine-containing waters if the individual has access to a sufficiency of iodine. If, however, the iodine supply is deficient or the utilization of iodine in the thyroid is disturbed through excess of dietary calcium or for some other reason, then the goitrogenic action of fluorine can manifest itself.

From the results of iodine determinations on more than 700 samples of water collected from goitrous and goitre-free areas, Szabó, Remenár & Demeczky[531] established without doubt that endemic goitre in Hungary is mainly due to iodine deficiency; the degree of hardness of water may also play a part. Independently of hardness or other factors, complete freedom

During his surveys in the district surrounding Ostrava in the extreme north of Moravia, Doleček [538] found a relatively large number of goitres associated with hypertension and other related disturbances. Doleček is among those who stress the importance of goitrogenic factors in the local foods and the need to employ rational prophylaxis.

Farther east, in Slovakia proper, goitre has been the subject of special study in Banska Bystrica [561] and in the Zitný Ostrov area immediately south-east of Bratislava where Slovakia abuts on Austria and Hungary between Vienna and Budapest. This focus is noteworthy inasmuch as the disease is more prevalent in the lowlands than in the surrounding mountains (Tománek; [565] Podoba, Németh & Grmelová; [553] Németh & Podoba [551]).

Following an extensive survey of the Zitný Ostrov area by the Bratislava Institute of Endocrinology in 1949, iodized salt was introduced in October 1950, first at a level of 1 in 200 000 and later at a level of 1 in 100 000. A resurvey carried out in 1954 on 17 750 persons of both sexes, ranging in age from 6 to 20 years, showed that there had been a distinct recession of the endemic, a decrease in the number of nodular cases, and a striking diminution in the size of local goitres (Németh & Podoba [551]).

Finally, in the extreme east of Czechoslovakia there lies Carpathian Ruthenia—now part of the Ukraine—where, in the vivid description of Suk, [567] goitre and its consequences (cretinism and myxoedema) may be seen at their worst. Here, the most wretched centres are the poor villages, in which, during the unfavourable winter months, the people live an unhealthy life in dark and cold unventilated huts. They consume large quantities of cabbage—raw cabbage, pickled cabbage, boiled cabbage and cabbage water. Indeed, cabbage is the staple diet. The goitrogenic effect of cabbage is revealed in the data collected by Suk in a number of out-of-the-way villages in the Carpathian highlands (see Table VI)

It is seen that the percentage of cases without goitre is much higher in all villages taken together than it is in the three villages where the consumption of cabbage is excessive

TABLE VI GOITRE PREVALENCE IN CHILDREN AGED 6 TO 14 YEARS IN SOME VILLAGES IN THE CARPATHIAN HIGHLANDS

Results of examination	All villages taken together			Three villages with excessive cabbage diet		
	number	percentage		number	percentage	
Without goitre	136	25 2		25	9 1	
Slight goitre	262	48 6	74 7	151	54 9	90 9
Medium goitre	100	18 5		67	24 4	
Large goitre	41	7 6		32	11 6	
Total examined	539			275		

decreased since the removal of people from the most seriously affected areas, nevertheless, prevalence remains high and presents a grave health problem, especially among children in upland areas The systematic use of iodized salt is strongly urged by the authorities

With the object of measuring the prophylactic effect of iodized salt administered over a period of years, Šilink, Reisenauer & Chaloupský[562] recently (1959) evolved a procedure to solve the problem of uniform and objective mapping of goitre The value of their method has been demon-

[illegible]

tions on the standardization of iodized salt and on the means of removing influences affecting its prophylactic efficiency have been made by Reisenauer & Likar[557] and by Šilink & Reisenauer.[561]

Moravia, the central part of Czechoslovakia, is heavily goitrous, particularly in the north. Local goitrogenic factors have been investigated by Šilink & Maršíková,[560] who determined thiocyanate values in the blood of volunteers from Šumperk in northern Moravia and Roudnice in Bohemia, two districts where goitre is rife. These values are higher in autumn, when the consumption of fruit and vegetables is greatest, than in the spring, and there is a direct relationship between the amount of thiocyanate in the blood and the degree of thyroid hyperplasia.

This does not mean, however, that thiocyanate itself is the goitrogenic factor, because the serum thiocyanate values in the goitre subjects from Šumperk and Roudnice are no higher than those found in subjects who had been given less than 0.1 g of potassium thiocyanate by mouth for long periods without the thiocyanate having any goitre-producing effect whatever. Šilink & Maršíková argue, therefore, that the foods consumed by the inhabitants of these districts contain not only a substance capable of raising the blood thiocyanate level, but also a specific goitrogen which they have not been able to identify

Podoba et al.[536] found a significant difference in the weight and histological picture of thyroids from rabbits fed raw cabbage alone, and from those fed mixed vegetables of the *Brassica* genus, both raw and cooked. The goitrogenic effect of the cooked mixed vegetables was lower than that of the raw mixed vegetables and significantly lower than that of raw cabbage.

Vomela[572] has studied the Holešov and Fryštát areas of eastern Moravia in great detail In the mountains, extreme forms of goitre and cretinism are common; 80% to 90% of the inhabitants are affected in some villages. Here, the general picture is definitely one of hypothyroidism On the Moravian plains, on the other hand, goitre also occurs but is accompanied by tachycardia, exophthalmos and other symptoms of hyperthyroidism. Zones of intermediate altitude show goitres of both types, even within one family.

During his surveys in the district surrounding Ostrava in the extreme north of Moravia, Doleček [538] found a relatively large number of goitres associated with hypertension and other related disturbances. Doleček is among those who stress the importance of goitrogenic factors in the local foods and the need to employ rational prophylaxis.

Farther east, in Slovakia proper, goitre has been the subject of special study in Banska Bystrica [561] and in the Zitný Ostrov area immediately south-east of Bratislava where Slovakia abuts on Austria and Hungary between Vienna and Budapest. This focus is noteworthy inasmuch as the disease is more prevalent in the lowlands than in the surrounding mountains (Tománek; [568] Podoba, Németh & Grmelová; [555] Németh & Podoba [551])

Following an extensive survey of the Zitný Ostrov area by the Bratislava Institute of Endocrinology in 1949, iodized salt was introduced in October 1950, first at a level of 1 in 200 000 and later at a level of 1 in 100 000 A resurvey carried out in 1954 on 17 750 persons of both sexes, ranging in age from 6 to 20 years, showed that there had been a distinct recession of the endemic, a decrease in the number of nodular cases, and a striking diminution in the size of local goitres (Németh & Podoba [551]).

Finally, in the extreme east of Czechoslovakia there lies Carpathian Ruthenia—now part of the Ukraine—where, in the vivid description of Suk,[567] goitre and its consequences (cretinism and myxoedema) may be seen at their worst. Here, the most wretched centres are the poor villages, in which, during the unfavourable winter months, the people live an unhealthy life in dark and cold unventilated huts. They consume large quantities of cabbage—raw cabbage, pickled cabbage, boiled cabbage and cabbage water. Indeed, cabbage is the staple diet. The goitrogenic effect of cabbage is revealed in the data collected by Suk in a number of out-of-the-way villages in the Carpathian highlands (see Table VI)

It is seen that the percentage of cases without goitre is much higher in all villages taken together than it is in the three villages where the consumption of cabbage is excessive

TABLE VI GOITRE PREVALENCE IN CHILDREN AGED 6 TO 14 YEARS IN SOME VILLAGES IN THE CARPATHIAN HIGHLANDS

Results of examination	All villages taken together			Three villages with excessive cabbage diet		
	number	percentage		number	percentage	
Without goitre	136	25 2		25	9 1	
Slight goitre	262	48 6	74 7	151	54 9	90 9
Medium goitre	100	18 5		67	24 4	
Large goitre	41	7 6		32	11 6	
Total examined	539			275		

The foregoing is but an outline of the goitre problem in Bohemia, Moravia and Slovakia. Medical literature of Czechoslovakia in recent years is rich in research on regional and etiological problems, of which only bare mention is possible here· Németh,[550] and Németh & Štukovský[552] on the retardation of bone development among children in goitre districts; Šilink et al[563] and Reisenauer, Šilink & Röhling[557] on the iodine metabolism of people in goitrous areas of Bohemia and Moravia; Langer and his colleagues[547-549] on the role of calcium and other dietary factors in the genesis of goitre in Czechoslovakia, Verner[569] on the inferior intelligence and mental capacity of children in goitrous regions; and Štukovský et al[565, 566] on the parallelism between human and animal goitre in western Slovakia.

Germany

Proceeding from the south to the north of Germany, it is possible to distinguish five main goitre zones one extending from Baden-Baden and the mountains of Breisgau and the Black Forest eastwards through Wurttemberg and southern Bavaria to the Austrian border; one in the Vogtland and Erzgebirge on the north-western frontier of Czechoslovakia; one stretching from the borders of Luxembourg north-eastwards along the Hunsruck and Taunus ridges through Hesse and Lower Franconia into Thuringia, one comprising Munsterland, parts of Westphalia, and the Bergische Land near Dusseldorf; and one in Brandenburg, extending from the region of Cottbus south-eastwards into Polish Silesia

The first of these zones includes the Kaiserstuhl area, the valley of the river Kinzig and the towns of Wolfach and Freudenstadt in the Black Forest, the towns of Hechingen and Geislingen in Wurttemberg, and a large number of places along the Austrian frontier between Lake Constance and Salzburg Among these southern Bavarian centres are Lindau, the Algauer Alps, Kempten, Landsberg, Schongau, Weilheim, Garmisch, Wolfratshausen, Tolz, Ebersberg, Miesbach, Traunstein, Pfarrkirchen and Berchtesgaden Goitre is also said to occur in the Bayrischer Wald along the north bank of the Danube between Regensburg and Passau

The second important zone lies between Plauen and Dresden It covers the Vogtland and the north side of the Erzgebirge and takes in Auerbach, Freiberg, Chemnitz, Oelsnitz, Schneeberg, Marienberg, Zwönitz and Annaberg.

In the third distinctive area, incidence is not excessively high but there are, nevertheless, some well-marked goitre centres Between Luxembourg and Koblenz the disease occurs in the Eifel district north of the Moselle river—notably, at Prum, Bitburg and Wittlich On the south of the Moselle, the town of Bernkastel and the neighbouring ridge of the Hunsrück are affected. Across the Rhine to the east of Koblenz there is goitre within a

circle drawn through Siegen, Giessen, Wiesbaden and St Goarshausen. This includes the Westerwald and the Taunus country immediately north of Wiesbaden where Königstein is a known focus. A traveller proceeding north-eastward from Siegen to Kassel would find goitre cases at Wittgenstein, Biedenkopf, Frankenberg, Fritzlar, Rotenburg and Melsungen. In the Mannheim-Frankfurt area there is goitre on the Odenwald and in the Spessart country, the town of Heppenheim to the north of Mannheim deserving special mention. Farther east, one finds the disease on the upper Tauber river, at Rothenburg in Middle Franconia, along the Steiger Wald, where Iphofen is a well-known centre, and at Gersfeld in the Rhöngebirge west of Meiningen. In Thuringia, the towns of Weissensee and Schmalkalden are said to be affected.

Fourthly, there is an area of slight endemicity in the Duisburg—Dortmund—Dusseldorf triangle and in the Bergisches Land, a region which rises in plateau-like terraces from the Rhine near Dusseldorf. The nature of thyroid disorder here has been described by Leicher.[610] During their post-war investigation of the nutritional status of children in the British Zone of Germany, Widdowson & McCance[627] found cases of thyroid enlargement in the municipal orphanages at Duisburg and Wuppertal-Vohwinkel

The fifth zone is found in the far east of Germany. It begins at Guben and Cottbus and extends south-eastwards to join the goitre belts of south-west Poland and northern Czechoslovakia Goitrous localities of special note in this region are Spremberg and Hoyerswerda

Throughout the past hundred years the geographical distribution of goitre in Germany has remained fairly constant, but the intensity of the disease has been subject to marked fluctuation After the First World War, German physicians reported an increase in prevalence all over the country, even in areas normally goitre-free, like Nuremberg, the Ruhr district and the North German Plain By the end of the 1920's this outbreak had subsided The same happened after the Second World War An upward trend in the frequency of thyroid disease became noticeable around 1942. Between the end of the war and the close of 1950 this had developed into an extensive epidemic, much more widespread and severe than that which occurred after the 1914-18 war. The following figures given by Ligdas[611] are typical of many reports They relate to schoolchildren in Dresden and other towns in that area of Saxony.

	Goitre rate (%) 1948-49	1949-50	1950-51
School beginners	9 1	11 9	14 4
Fourth-year scholars	8 7	19 1	19 8
" Confirmands "	11 6	19 0	22 6
Trades School	13 0	18 0	23 6
High School	12 2	16 2	22 8
Trades High School	16 2	20 4	37 7

These post-war goitre waves are due, as is apparent from many reports, to dietary deficiency during the war period. Proof of this is found in the fact that certain well-fed groups of people—for example, cooks, interpreters and occupying troops—escaped the goitre wave. This is also borne out by Haubold's investigation of schoolchildren in Bavaria, where the goitre rate rose to 42%, while only 9% of children in occupying American families were affected.

Arguments have been advanced by Haubold[600-603] that the specific dietary deficiency responsible for the post-war goitre wave is a decreased intake of vitamin A and carotene. His goitre surveys in the Weilheim district of Upper Bavaria show that in villages where the vitamin-A and carotene contents of butter and herbage are exceedingly low, the goitre rate is more than double that in villages where these dietary factors are substantially more plentiful The goitres occurring under circumstances of vitamin-A deficiency are of the hyperthyroid type, and it has been shown by Bukatsch, Haubold & Lackner[582] that treatment with vitamin A or carotene causes regression of the goitre and amelioration of the signs of hyperthyroidism.

On the other hand, Ligdas[611] maintains that, in spite of the interesting observations by Haubold, deficiency of iodine in natural form remains the factor chiefly responsible for the post-war goitre waves. At the beginning of the Second World War the German people were consuming an average of 12 kg of sea-fish per head per annum During the first five years following the end of the war the people hardly ever saw sea-fish at all, according to Ligdas. The connexion between agricultural food production and the occurrence of goitre among schoolchildren in the Berlin area has been examined in detail by Habermann[596-599] in an excellent series of papers

In the years between the two wars, prophylaxis by iodized salt, "Vollsalz" as it is called in Germany, had been tried in many areas; but owing to the fear of possible harmful effects (now known to be without foundation) more propaganda against the use of iodized salt has been advanced in Germany than in any other country in the world. Gloel,[593] Medical Officer of Health at Landsberg in Bavaria, reported in 1934 that as a result of the almost exclusive use of iodized salt a strong, healthy, non-goitrous generation was growing up in the goitrous districts of Bavaria, notably at Kempten. He deplored the fact that in his own district the practice had been abandoned for fear of iodine poisoning Where iodized salt had been in general use since 1924, Gloel did not find a single case of thyroid enlargement among pupils of a school he inspected in 1930 Four years later, however, owing to the withdrawal of iodized salt, 75% of the children in the same school were suffering from thyroid enlargement. He also records that provincial teachers had noticed a corresponding decline in the average intellectual capacity of children beginning school life.

Today the situation in southern Bavaria is little better than in 1934, and a strong plea for the re-introduction of iodized salt has recently been made by Bauer.[578] In co-operation with five medical colleagues he examined a total of 45 818 schoolchildren in the localities of Miesbach, Chiemgau, Traunstein, Berchtesgaden, Pfarrkirchen and Donauwörth, and was "shocked" to find goitre rates of 80% and even more in some places. In the Donauwörth area, for example, 93% of young people in Egelstetten had goitre, 61% in Ellgau, and 77% in Genderkingen, while Donauwörth itself, with 23%, was relatively immune.

Hundreds of papers have been written about goitre in Germany Entries 573 to 628 in the bibliography at the end of this chapter are selected as dealing more especially with distribution and prevalence

Switzerland

Endemic goitre has long been a serious health problem in Switzerland. Practically all parts of the country are prone to the disease, and in many localities it is markedly associated with mental deficiency, deaf-mutism and other disorders Indeed, the burden of cretinism has been a heavy charge on public funds. In 1923 the Canton of Bern alone, with a population of little more than 700 000, had to hospitalize 700 cretins incapable of any social life.

Cantons where the incidence has always been high are Aargau, Zurich, Schaffhausen and Thurgau in the north; Appenzell, St Gallen and Graubünden in the east; Bern, Luzern and Uri in the centre, and Fribourg and Valais in the south-west There is less goitre in the north-western cantons, Basel, Solothurn and Neuchâtel

Thanks, however, to the official encouragement given to the general use of iodized salt the situation has greatly improved in recent years. Goitre rates have fallen steeply and deaf-and-dumb institutions have been closed or diverted to other purposes (Wespi [675, 678]). Recruitment statistics provide unmistakable evidence of this downward trend Table VII (Schaub [665])

TABLE VII INCIDENCE OF GOITRE AMONG ARMY RECRUITS IN SWITZERLAND

Year	Number of men examined	Number of men exempt on account of goitre	Number of goitres per 1000
1900	26 285	2 451	93 2
1905	26 448	3 093	116 9
1914-18	151 106	3 403	22 5
1921	32 838	1 817	55 3
1925	39 681	1 229	30 9
1935	29 627	338	11 4
1939-45	228 101	340	1 5
1945	31 654	21	0 6
1947	31 366	23	0 7

shows that between the years 1925 and 1947 the number of exemptions from military service on account of goitre fell from 31 per thousand to less than 1 per thousand. The recession began with the introduction of iodized salt in the early 1920's and has been maintained ever since

The same decline is seen in the goitre statistics relating to young people. For example, an examination in 1937 of schoolchildren in the Canton of Valais—a region particularly affected—gave the results shown in Table VIII (Bayard [629])

TABLE VIII INCIDENCE OF GOITRE AMONG SCHOOLCHILDREN IN THE CANTON OF VALAIS

Period	Normal thyroids (%)	Palpable thyroids (%)	Enlarged neck (%)	Pronounced goitres (%)
1920 (Before introduction of iodized salt)	28 8	54.3	14 9	2 0
1934 (Ten years after introduction of iodized salt in 1924)	70 5	27.3	2 1	0 15

At three towns in the valley of the Broye, a singularly goitrous area of the Canton of Vaud, where 20% to 40% of conscripts were usually rejected, Messerli [653] has shown that between 1921 and 1951 thyroid enlargement in children has very greatly decreased The statistics are as follows; they should be considered in the light of the fact that since 1924 100% of all salt consumed by the people throughout the Canton of Vaud has been iodized

Locality	*Goitre rate (%)* 1921	1937	1951
Avenches	78 9	24 1	7 1
Payerne. . .	78 0	22 4	4 0
Moudon	73.5	18 3	4.9

Similar results have been obtained from many different parts of Switzerland, and all responsible investigators agree that the descending curve of incidence can be correlated with the period over which supplementary iodine has been introduced into the diet of the population The sale of salt is not a federal but a cantonal matter, in accordance with the salt laws of individual cantons. Accordingly, the introduction of iodized salt has differed markedly from canton to canton, both in point of time and in regard to the quantity sold. Goitre statistics coincide precisely with these facts. Thus, the reduction in the number of conscripts rejected on account of goitre begins much earlier in those cantons which introduced prophylaxis in the years 1922, 1923 or 1924 than in those which did not introduce it until 1929 or 1930. Furthermore, as is evident from the statistics shown in

TABLE IX RELATION BETWEEN CONSUMPTION OF IODIZED SALT AND REJECTION OF ARMY RECRUITS ON ACCOUNT OF GOITRE

Cantons *	Average consumption of iodized salt per canton, expressed as a percentage of total salt consumed				Average number of rejections on account of goitre, per 1000 recruits called up			
	1910-22	1923-32	1933-42	1943-47	1910-22	1923-32	1933-42	1943-47
1 to 9	Nil **	75 3	96 5	96 0	36 3	16 7	1 8	0 3
10 to 17	Nil	30 0	68 1	86 8	30 1	21 2	6 0	0 7
18 to 25	Nil	8 5	25 1	53 5	35 2	22 2	8 7	1 5

* 1 to 9 Nidwalden, Vaud, Zug, Schaffhausen, Schwyz, Obwalden, Valais, Neuchâtel, and Appenzell Ausser-Rhoden
10 to 17 Ticino, Glarus, Uri, Appenzell Inner-Rhoden, St-Gallen, Geneva, Graubünden, and Thurgau
18 to 25 Zurich, Bern, Luzern, Fribourg, Solothurn, Basel-Stadt, Basel-Land, and Aargau
** The single exception is the Canton of Appenzell Ausser-Rhoden, where iodized salt was introduced in 1922

Table IX (Schaub [665]), the magnitude of the reduction is directly parallel to the absolute amount of iodized salt consumed.

In his assessment of the results of goitre prophylaxis in Switzerland published by the World Health Organization in 1953, Nicod [657] remarks that the only canton which has almost entirely resisted the use of iodized salt, that of Aargau, is the one which still rejects the largest number of young people on account of goitre Nicod's later review [658] (1957) of the progress of goitre prevention by iodized salt in Switzerland re-emphasizes emphatically its effectiveness and safety.

The dental caries problem in Switzerland has prompted Wespi and his colleague Eggenberger [676, 677, 680] to recommend the manufacture and distribution of a dual-purpose salt enriched with 200 mg of sodium fluoride and 10 mg of potassium iodide per kilogram of salt

The literature on Swiss goitre is extensive; in the bibliography at the end of this chapter, only a few of the more important epidemiological studies are cited [629-682]

Italy, Sicily and Sardinia

The many descriptions of goitre and cretinism to be found in the classics and in Italian literature of the Middle Ages show that thyroid disease has been a problem in Italy from earliest times Indeed, its seriousness and persistence into the nineteenth century prompted one of the first and most competent goitre surveys ever made under government auspices This was the Commission of nineteen members appointed in 1845 by King Carlo Alberto of Sardinia to investigate the extent, nature and causes of the disease throughout his Kingdom, which in those days comprised the provinces of Savoy, Nice, Piedmont, Genoa and the island of Sardinia.[771]

shows that between the years 1925 and 1947 the number of exemptions from military service on account of goitre fell from 31 per thousand to less than 1 per thousand. The recession began with the introduction of iodized salt in the early 1920's and has been maintained ever since.

The same decline is seen in the goitre statistics relating to young people. For example, an examination in 1937 of schoolchildren in the Canton of Valais—a region particularly affected—gave the results shown in Table VIII (Bayard [629]).

TABLE VIII. INCIDENCE OF GOITRE AMONG SCHOOLCHILDREN IN THE CANTON OF VALAIS

Period	Normal thyroids (%)	Palpable thyroids (%)	Enlarged neck (%)	Pronounced goitres (%)
1920 (Before introduction of iodized salt)	28.8	54.3	14.9	2.0
1934 (Ten years after introduction of iodized salt in 1924)	70.5	27.3	2.1	0.15

At three towns in the valley of the Broye, a singularly goitrous area of the Canton of Vaud, where 20% to 40% of conscripts were usually rejected, Messerli [653] has shown that between 1921 and 1951 thyroid enlargement in children has very greatly decreased. The statistics are as follows; they should be considered in the light of the fact that since 1924 100% of all salt consumed by the people throughout the Canton of Vaud has been iodized.

Locality	*Goitre rate (%)* 1921	1937	1951
Avenches	78.9	24.1	7.1
Payerne	78.0	22.4	4.0
Moudon	73.5	18.3	4.9

Similar results have been obtained from many different parts of Switzerland, and all responsible investigators agree that the descending curve of incidence can be correlated with the period over which supplementary iodine has been introduced into the diet of the population. The sale of salt is not a federal but a cantonal matter, in accordance with the salt laws of individual cantons. Accordingly, the introduction of iodized salt has differed markedly from canton to canton, both in point of time and in regard to the quantity sold. Goitre statistics coincide precisely with these facts. Thus, the reduction in the number of conscripts rejected on account of goitre begins much earlier in those cantons which introduced prophylaxis in the years 1922, 1923 or 1924 than in those which did not introduce it until 1929 or 1930. Furthermore, as is evident from the statistics shown in

who have written especially about these regions are Pighini,[759] Muggia,[751 758] Fiorio,[732] Cancellara,[699] Paccagnella,[753] and Turri.[780] Their investigations indicate that in the area between the Alps and the river Po thyroid enlargement is found in 20%-30% of schoolchildren. In high mountain districts these figures may rise to 50%-60% and in certain communities may reach even 70%-80% Indeed, rates of 100% are not unknown (Ambrosi [684]).

In the great north-central plains thyroid disease is much less severe, but acute episodes do arise from time to time as, for instance, that recently described by Denes & Andreotti [723] at Carmignano di Brenta, a municipality in the grape and cereal-growing country 9 miles north-east of Vicenza in Padua Province. Here, signs of thyroid enlargement were first noticed in 1947, attained their greatest severity by 1950, and then disappeared.

Apart from the main Alpine belt and the sporadic outbreaks in the northern plains, goitre also occurs in the Ligurian Apennines immediately north of Genoa (Bagnasco [687]). A large number of places in the Etruscan Apennines due south of Modena are also affected. For instance, Mucci [752] records rates of between 10% and 60% among boys and girls at Montese, Magreta, Guiglia, Mirandola and Riolunato The etiology of acute goitre in the valleys of the Secchia and Dolo rivers has been investigated by Pighini & Gualdi;[760] and Businco [698] has described at length all the circumstances surrounding a goitre focus of unusual severity in the district of Sestola near Monte Cimone. Somewhat further south is the Province of Pistoia, where an epidemic of goitre in young people occurred in the war years 1941 to 1946 (Bizzarri [693]) All sorts of theories have been advanced to account for this outbreak—nitrites and sulfur compounds in the water-supply, emotional factors due to war stress, and so on—but it seems that food deficiency during the period of emergency is the most likely cause.

In Tuscany, also, epidemic goitre has been noted by Nassi & Calamari [757] in the region of Montespertoli, an upland village about 16 miles south-west of Florence Clinical examination of the children led to the conclusion that an infection acting on a population in a state of nutritional deficiency and border-line thyroid adequacy was the cause The most recent accounts of goitre in the Province of Florence are those by Magherini & Zecchi [741] and Magherini et al.[742] They examined 1756 children aged 6 to 14 years in the communes of Londa, San Godenza, Vicchio di Mugello, Pontassieve and Rignano sull'Arno, and found goitre rates varying from 36% in Londa to 70% in Rignano Goitre was evident in 69 out of 97 mentally subnormal and in 77 out of 134 mentally normal children

Due east of Florence towards the Adriatic coast, a centre of severe endemic goitre lying in the upper valley of the river Conca on the eastern slopes of Monte Carpegna has been minutely described by D'Alo [719] The affected area, which is horseshoe-shaped, is bounded by the Faggiola and San Paolo on the east, by Monteboaggine and the Carpegna massif on the south, and by Monte Palazzuolo and Costagrande on the west. The most

Modern reviews of the goitre problem in Italy have been undertaken by Ciocchi [705 707] and by Costa and his school,[710 717] both of whom refer particularly to the outbreaks of acute goitre that occurred in Piedmont during the war years of 1940-1945. According to Costa & Mortara,[712] endemic goitre, widespread in the last century and in the first decade of the present, subsequently began decreasing in the north of Italy while increasing somewhat in central and southern parts of the country About 20 years ago, however, the phenomenon of epidemic goitre made its appearance in the north, this has given rise to much research to determine its cause and its relationship to the endemic type In Costa's view, the endemic noxa in Italy cannot be identified with goitrogenic factors or iodine deficiency in local foods and waters; no substantial differences have been shown between endemic and non-endemic areas.

Cerletti [702] is convinced that even today five million people in Italy (i e, 10% of the population) are affected by thyroid disease. The literature of Italian goitre, of which we cite 100 papers,[683 782] is certainly the most extensive of any country in the world

Geographically, the endemic occurs to a varying degree throughout the whole of the Alpine region in the north of the country, in a semi-circular belt extending from the Ligurian Alps through Piedmont, Lombardia and Trentino to Venezia in the east The disease is found not only in the upland valleys, but also in the plains north and south of the river Po, although to a much smaller extent.

In the Region of Piedmont, intensively studied by Cerruti [701] and by Mortara,[748] the places particularly affected are, first, the towns of Cuneo and Saluzzo, where outbreaks of acute goitre occurred among troops in 1940-41 (Anglesio [686]) Children from various schools in the districts of Cuneo, Saluzzo and Alessandria were recently (1957) examined by Mortara & Martinetti [751] who found that the disease still affects the rising generation in these places Farther north are the district of Aosta and the valley of the Dora Baltea at the foot of Mont Blanc, long a noted centre. It has been surveyed fully by Trikurakis [776 778] and by Raggi & Marocco,[767, 768] and was the focus of an outbreak described in 1948 by Vogliazzo & Forni [781] Nearby, is the Canavese region, the chief centre of which is Ivrea where acute forms of goitre in adults have been noted by Maggiorotti.[740]

In this same general area goitre is seen at Vercelli and in the valleys of the Sesia and Ticino rivers. Also affected are the Province of Varese between Lakes Maggiore and Como; the town of Como itself; the valley of the river Adda and the mountains of Valtellina and Sondrio in the extreme north; the alpine hinterland of Bergamo and Brescia, including Breno and the valley of the Chiese; the valleys of the Peio, Sole and Rabbi west of the Trento-Bolzano axis; the Region of Trentino-Alto Adige (which includes the Dolomites); Valsugana; the neighbourhood of Belluno; the Carnic Alps and the district around Udine in Venezia-Giulia. Authorities

adults and 49% of children showed thyroid enlargement, and 58% of adults and 41% of children, dental fluorosis. No direct relationship between the two conditions could be established; the greatest severity of fluorosis was seen in people with no thyroid abnormality.

In Sardinia the prevalence of goitre among schoolchildren has been studied in the Province of Cagliari by Corda[709] and by Desogus[726] In the middle-west of the country, goitre is endemic in the town of Santu-lussurgiu and its surroundings, but cretinism is unknown (Ferraris et al.[728])

At Sondrio and in the Valtellina goitre prophylaxis by iodized salt (1 50 000) had, by 1938, been in vogue for about fourteen years with good results (Lutrario;[738] Ambrosi;[684] Cerruti[701]) In that time the number of cases showing obvious enlargement fell from 57% to 1 4% Besides the general decrease in thyroid size there was a lowering of the infant-mortality rate and improved mental alertness among children Iodine preventive measures have also been applied in the Valle d'Aosta by a committee set up by the public health authorities of the Region Iodized chocolates, each containing 10 mg of potassium iodide, were distributed to schoolchildren at the rate of two per week, and in some schools open wide-mouthed bottles of tincture of iodine were exposed Good results were obtained from the chocolate tablets, but no benefit followed the exposure of iodine tincture.

Malta

D C Wilson (personal communication, 1955) says she has seen goitre in Maltese people who come from the north and west of the island where the water-supply is derived from wells It is of interest that waters obtained

Spain

There is a great deal of goitre in Spain Almost all mountainous districts are affected, some to a serious degree Particulars of the distribution are derived from four principal sources: (1) the 1927 report of the Commission of Inquiry on Goitre, set up by the Spanish Government in 1921 under the direction of Marañón;[791, 792] (2) the long and important series of investigations (1947-56) conducted under the leadership of Ortiz de Landázuri of the Faculty of Medicine, Granada, and the Department for Goitre Prophylaxis, Board of Health;[783, 795 808, 813 815] (3) the reports[786, 810] of the well-known Barcelona endocrinologist Cañadell, in collaboration with the Swiss investigators Eugster & Dieterle; and (4) the accounts of goitre in the Province of Sevilla by Rivero Fontán and co-workers[781, 811] The history of goitre in Spain has been written by Greenwald[787] who sheds

important inhabited centre in the locality is Montecerignone. Extreme poverty, malnutrition, wretched living conditions, and unhygienic ill-lit and badly ventilated houses are the unhappy lot of the people in this area.

Goitre is endemic in Umbria and throughout the Marches in central Italy, especially along the river Tenna in the Montegallo area and in other parts of the province of Ascoli Piceno (Scocciant;[772] Balice;[688, 689] Pitzurra,[761] Pitzurra & Modolo;[764] Tarozzi[774])

In the west, the disease is known in the Latium uplands in the Viterbo area (but not in Viterbo itself) to the north of Rome (Cerletti[702]) and at Giulianello in the parish of Cori to the south of Rome. This latter focus has been carefully studied by Di Porto & Antoniotti,[727] who point out that the district is extremely volcanic and suggest that the prevalence of goitre may be due to an excess of silica in the local foods and waters, a theory in agreement with that of Trikurakis[778]

Very high goitre rates (40%-80%) are reported by D'Amora[720] from villages in the Sorrento peninsula. At Lauro, a village in the uplands about 30 miles east of Naples, 9% of boys and girls between the ages of 5 and 14 years were found by Sainsbury[769] to have goitre. The main formation in the area is limestone and the water is deep spring with the low iodine content of 2.1-2.2 μg per litre. The dietary standards are poor and the consumption of fish negligible. On the opposite side of the country, goitre centres are found both on the sea-shore and in the hills of the Gargano peninsula (Cerletti[702]). In Lucania thyroid enlargement is noticeable at several places, particularly in Potenza Province (Ambrosi;[683] Calbi;[697] Pitzurra & Ponzio,[765] Barbieri,[691] Pitzurra, Modolo & Mori[763]). Throat measurement of elementary schoolchildren at Palazzo San Gervasio, a town lying between Canosa and Potenza, has enabled Cancellara[698] to calculate an index of thyroid enlargement which he finds useful for determining the incidence of thyroid disease in a given section of the population.

In the extreme south of Italy, a little-known area of endemic goitre has been described by Criscenti[718]. This includes the districts of Savuci, Taverna and Maranise, in the Province of Catanzaro, where the people live very largely on chestnuts and rye, and where the soils are derived from granitic rocks and archaean crystalline schists. At Taverna 93% of schoolchildren were found to be sufferers; at Savuci the rate was 77%.

Foci of endemic goitre and cretinism in Sicily have been described by Coppola[708] who refers especially to Nicosia in the Province of Enna as a noted centre. A prevalence of 29% among schoolchildren in the municipality of Barcellona Pozzo di Gotto on the north-east seaboard was observed by Spadaro & Alfano[773] in 1955. Dental fluorosis was noticeable in a high percentage of the goitre carriers. A re-survey of the area by Previtera, Molino & Pagano[766] in 1958 revealed lower rates, due it is believed to improved water supply. In 1957, Tempestini[775] inspected 500 inhabitants of the village of Motta Camastra (Province of Messina); of these, 42% of

whence it spreads over the Asturias, Oviedo, León, and into the valleys of Galicia In the extreme north-western section the endemic is less severe than in the high valleys of the Pyrenees between Spain and France where, in addition to simple goitre, there is a good deal of cretinism and deaf-mutism. Cretinism is also a strong feature in the Asturias—an area which, according to Marañón,[792] has been studied in great detail by Goyanes and Cemiga. Here, numerous cases of goitre and cretinism occur near the sea as well as at higher levels

In central Spain goitre is found along the Sierra Gredos lying to the south of Ávila Province west of Madrid. In this area the valleys of the head-waters of the rivers Tormes and Alberche are particularly affected, as also is the valley of the Tiétar where the endemic has been studied in some detail by Martín Lázaro[791] West of this towards the Portuguese border, goitre is exceedingly prevalent in the Sierra de Gata Here, indeed, we find one of the most notorious goitre centres in the world—the region of Las Hurdes, a section of the Sierra de Gata covering the extreme northern tip of the Province of Cáceres.

Las Hurdes constitutes an incomparable field for the study of goitre. It is the most important focus in all Spain The area, mapped by Pérez-Vitoria,[809] is composed of three long narrow valleys of unbelievably rough and inhospitable country. The geological formation is exclusively of slate and has a sparse and unproductive vegetation The prevalence of goitre exceeds 25% and large numbers of the goitrous population are also cretinoid Cases of idiotism, deaf-mutism, infantilism and dwarfism are many, and not a single man from the district has been found fit for military service, either because of low stature or marked feeble-mindedness The whole region is one of tragic aspect and has given rise to numerous legends—often exaggerated no doubt—in the records of ancient and modern travellers and national writers (Legendre,[790] Marañón[791]) Other goitre areas in central Spain lie in the east towards the Mediterranean, they include the Province of Castellón de la Plana,[783] particularly the mountains of the Alto Maestrazgo, and a large part of the Province of Valencia

Southern Spain's most goitrous province is Granada, where the region of Las Alpujarras on the southward slopes of the Sierra Nevada is highly affected and has been studied in detail by the school of Ortiz de Landázuri.[788, 795 808, 813 815] Elsewhere in the south goitre is found in the north part of Sevilla in the neighbourhood of Constantina between the Guadalquivir and the Sierra Morena Cases are also encountered in the Sierra de Algodonales between the Provinces of Sevilla and Cádiz, and in the Serranía de Ronda on the west border of Málaga Province[784, 793, 811]

The outcome of a great deal of experimental work in the University of Granada has convinced Ortiz de Landázuri and his colleagues that iodine deficiency is the main cause of goitre in the Granada area. This assumption is based on the extremely low iodine content of the drinking-

interesting light on reasons for the comparative rarity of the disease among Jews.

From data acquired by provincial health inspectors, Ortiz de Landázuri and his colleagues have prepared a map showing, by a system of crosses, the comparative intensity of the endemic in those provinces in which the disease chiefly occurs[788, 803] The indications are as follows (provinces not mentioned are those for which no data are given on the map):

Northern Provinces

Province	Intensity	Province	Intensity
Lugo	++	Navarra	++++
Oviedo	++++	Huesca	++
Santander	++	Lérida	+
Vizcaya	++	Barcelona	++
Pontevedra	+	Zaragoza	+
León	+++	Tarragona	+
Zamora	+		

Central Provinces

Province	Intensity	Province	Intensity
Ávila	++	Guadalajara	+++
Madrid	+	Teruel	+++
Cáceres	++++	Albacete	+
Cuenca	++	Castellón	+
Badajoz	++	Valencia	+++

Southern Provinces

Province	Intensity	Province	Intensity
Sevilla	++	Jaén	++
Córdoba	+	Granada	++++
Cádiz	+	Almeria	+
Málaga	++		

In the north, a belt of very considerable intensity extends from Catalonia along the Pyrenees through the Cordillera Cantabrica and the Asturias to Galicia in the west. Tracing this in greater detail, we find goitre especially in the north-west of Gerona Province, where the regions of Ribas de Fresser and Camprodón provide many cases In the neighbouring Province of Barcelona there is much goitre in the Montseny area, in the Llusanés valley and in the country to the north of Berga. Conditions here are described by Eugster & Dieterle[786] as exceedingly reminiscent of those *in the foothills of the Swiss Alps, indeed, the people call the district "pequeña Suiza"* (little Switzerland). Incidence is highest in the deep intersecting valleys of the region, whereas the high tablelands are mostly free from the disease. Piulachs & Cañadell[810] have prepared a detailed goitre map of this area, and representative photographs of the Montseny goitres have been published by Draper Alfaras[785]

Moving westwards through Lérida Province, we find considerable goitre in the Valle d'Arán. In Huesca, the northern valleys of the river Cinca and its tributaries are well known to be goitrous. From thence the endemic extends through the Provinces of Navarra and Vizcaya into Santander,

Western Europe

Belgium

It seems to be generally agreed that goitre is not an outstanding problem in Belgium today, although there are earlier reports of its endemic occurrence in some of the high-lying southern districts towards the Ardennes and Luxembourg The comparative absence of goitre goes hand in hand with Clinquart's [825] observation that drinking-waters in Belgium contain more iodine than those in Switzerland

During the 1939-45 war, however, Brull [819] first drew attention to a changing incidence of thyroid disease in Belgium. He found that the basic metabolic rate of all goitre cases seen at his clinic in Liège showed a steady decline from an average figure of +21.9% in 1939 to +6 6% in 1942 This was confirmed by Bastenie [818] who, in comparing the number and severity of cases of thyroid disease observed at the St. Pierre Hospital, Brussels, in the years before and during the German occupation, found that whereas the incidence and severity of hyperthyroidism did not increase and may probably have decreased, there was a significant increase in the incidence of simple goitre at all ages but particularly in the age-group 15-25 years

The observed changes in incidence and severity are thought to be related to the quantity and quality of the diet, especially the wartime increase in the consumption of cabbage and related vegetables which contain substances of the thiourea group In this connexion it has been pointed out that if the increase in simple goitre in Belgium during the war was in fact comparable to the " cabbage " or " rape-seed " goitre of animal experiments, a reduction in severity might be expected in cases of toxic goitre on the same diet Such patients would, in effect, be treating themselves on the most modern lines If this is the correct explanation it leaves open the possibility that there was an actual increase in thyrotoxicosis in Belgium during the war, which was masked because the population was being simultaneously dosed with thiourea compounds taken in the diet.

The latest study of the distribution and frequency of goitre in Belgium is that by Brull & Dewart [826] who examined 54 000 army recruits Of these, only 1 3% showed thyroid enlargement at enlistment; and most of the cases were simple hypertrophy without either toxic or hypothyroid symptoms. Frequency increased from the coast to the east and south of the country, i e , towards the higher areas of La Fagne, the Ardennes, and Luxembourg

England and Wales

In his *Treatise on English Bronchocele*, Inglis [856] says that at one time goitre was as common in the Yorkshire dales as in Geneva or any of the Alpine valleys Children could be seen at play with pieces of black velvet tied around their necks—a superstition to ward off the goitre evil or charm it away.

waters from affected districts[796] and is confirmed by the fact that in the space of 16 months there was an over-all decrease in the goitre rate, from 60% to 33%, as a result of administering iodized salt (1 : 50 000) in an area of extreme endemicity[789]

Most recent results (1959) of mass prophylaxis with iodized salt in Spain are those of Ibáñez González et al.,[789] whose data refer to the Alpujarras region of Granada Applied to a population of 100 000 since February 1954 the general use of iodized salt has resulted in a progressive decrease in the goitre rate from 55% in 1953 to 33% in 1955 and 13% in 1958. Neither administrative inconvenience nor any harmful secondary effects were encountered

Portugal

The distribution of goitre in Portugal is best seen on the map published in 1950 following the national inquiry on endemic goitre instituted by the Director-General of Health.[818] Although nowhere exceptionally severe, the disease is endemic or of frequent occurrence in the following districts:

Northern Portugal Vinhais, Terras de Bouro, Mondim de Basto, Amarante, Penafiel, Baiao, Castro Daire, and Sátão. Cretinism is seen in Vinhais and Amarante.

Central Portugal To the east, the goitre belt of western Spain (Sierra de Gata) extends into the districts of Sabugal, Belmonte, Penamacor, Fundão, Castelo Branco, Oleiros, Proença-a-Nova, Mação, and Crato On lower ground to the west, nearer the sea, goitre occurs in Miranda do Corvo, Ancião, and Castanheira de Pera

Incidence is highest in the region of Castelo Branco, here goitres begin to develop in children of five or six years of age, whereas the great majority of cases in other parts of Portugal occur between puberty and the age of 50

South Portugal Goitre is seen in the neighbourhood of Montemor-o-Novo east of Lisbon, and there is a belt of mild incidence in the extreme south, covering the districts of Odemira, Ourique, Almodovar, Loulé and Tavira

In common with other countries the disease occurs much more frequently in females than in males, it often appears in various members of the same family; but in only four sufferers was it found to be associated with deaf-mutism. Goitre is known by several different words in Portugal. *Bócio* is the medical term, but ordinarily it is called *papeira* or *papo*; other familiar names are *garganta*, *lobo* and *papada*. Organic debility, emotional disturbances, prolonged anxiety, and peculiar qualities of soil and water are some of the factors to which goitre is attributed. There is a popular notion in Ourique that the disease is caused by drinking water that has passed over the roots of a fig-tree.

Other records[a] in the early medical history of English counties show that goitre and cretinism were prevalent in Norfolk, in the Manchester area, in Monmouthshire, in Cornwall and elsewhere There was a strong endemic centre in Weardale in the west of Durham, and cretins were notorious at Chiselborough in Somerset A local predilection for oatmeal cakes was believed to be responsible for goitre in Matlock And to this day the synonym "Derbyshire neck" brands that county as goitrous—albeit unfairly, for goitre has always been equally severe, if not more so, in Oxfordshire, Gloucestershire, Somerset and Dorset

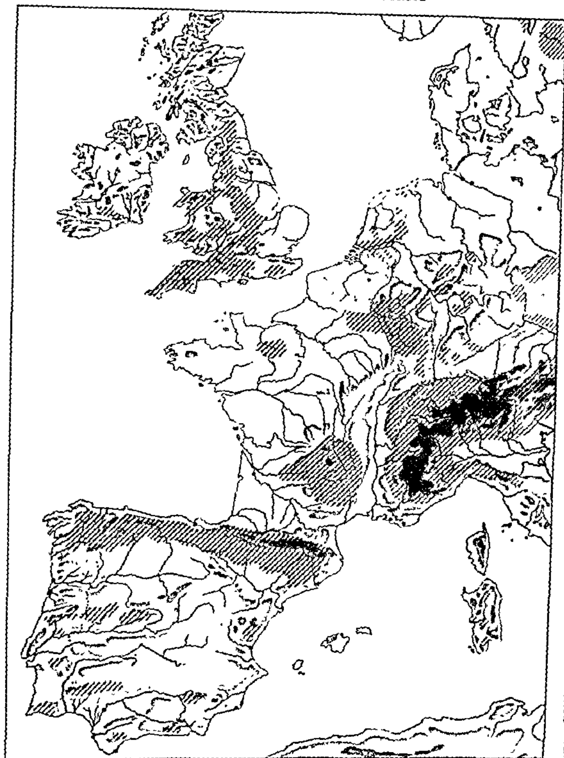
The first connected account of the geographical distribution of goitre in England is that by Berry,[836] who found thyroid enlargement moderately prevalent in the south-east of England, particularly in the Wealden area of Sussex and on the high ground around Horsham and towards Haslemere in Surrey. To the west and south-west the disease was conspicuous in Gloucestershire and in east and south Somerset There was a distinct seat of occurrence in the Warwickshire villages south of Leamington Farther east, a centre existed in Bedfordshire and there was evidence of goitre in Buckinghamshire and Hertfordshire In the midlands a considerable number of goitrous people were noticed in Staffordshire, Lancashire and Derbyshire From thence Berry traced the goitre belt northwards through Yorkshire to the junction of west Durham, Northumberland and Cumberland where there was a well-known endemic focus at the lead-mine district of Alston and the adjoining area of Weardale

A comprehensive all-England examination of 375 000 schoolchildren undertaken by the medical department of the Board of Education in 1924 [839] not only confirmed the goitrous areas delineated by Berry a quarter of a century earlier, but disclosed a trend of goitre incidence sufficiently disquieting to prompt the first official recommendation that "prophylactic administration of iodine to girls in some endemic areas of England and Wales might be desirable" [883] The over-all goitre rate revealed by the 1924 survey among schoolchildren of 12 years of age was 5 26% in boys and 13 33% in girls in areas of high prevalence, and 1 49% in boys and 4 41% in girls in the areas of low prevalence. But some places—notably, in Devon, Somerset, Oxfordshire, Northumberland and Durham—had goitre rates of 10% to 20% among boys and more than 30% among girls.

The prophylactic administration of iodine recommended by the 1924 survey was never given general effect; but during the inter-war years some attempt was made to introduce iodized chocolate and sweets in a few affected localities These measures, however, depended too much on the unaided efforts and enthusiasm of individual public health officials and consequently lacked the continuity which support from a central authority alone can ensure

[a] See reference 832, 834 835, 837, 838 843, 845, 847 851, 853, 856, 857, 859, 860 862-865, 868, 872, 873, 875-880, 882, 888 890, and 893 in the bibliography

FIG 4 WESTERN AND SOUTHERN EUROPE



The red hatching indicates the areas where endemic goitre has been found

compulsory use of iodized salt and suggests that it would possibly be helpful to make thyroid disease notifiable. The prevalence of goitre in two contrasted South Wales communities (Rhondda Fach and the Vale of Glamorgan) has been studied by Cochrane & Miall,[810] with the assistance of W. R. Trotter

Schools of north Oxfordshire in which the Medical Research Council team [871] recorded high goitre rates in 1944-48 were re-examined in 1958 by the same clinical methods and classification. The area in question lies on a belt of limestone and marl extending through the county from Witney to Banbury Hughes, Rodgers & Wilson,[854, 855] who undertook the second survey, found that the previous rate of 26 9% in girls had significantly increased to 40 4%. No significant change was found in the rate for boys; this remained at 14 8%

The iodine level in milk from farms in north Oxfordshire was compared with that of milk from farms in Wales and Essex, no significant difference was found It is suggestive, however, that the water drunk by cows in non-goitrous Essex contained from 18-117 µg of iodine per litre whereas in Oxfordshire and Wales, both of goitrous tendency, the corresponding values were 1 7-5.3 µg per litre and 2 2-2.9 µg per litre, respectively

In 1944 [850] and again in 1948 [871] the Goitre Subcommittee of the Medical Research Council urged the general adoption of iodized salt throughout the United Kingdom as a means of preventing goitre The level recommended is 1 part of potassium iodide in 100 000 parts of all salt, or 1 part in 40 000 parts if only packeted table salt is to be iodized In 1950 the Government of the day seemed disposed to fulfil this recommendation; but no action followed All that has been sanctioned and carried into effect is the addition of potassium iodide to the vitamin tablets issued by the Ministry of Health to expectant and nursing mothers.

Scotland

The survey by the Medical Research Council [871] mentioned in the section on England and Wales confirmed the well-known fact that the content of iodine in drinking-water is a determining factor in the distribution of endemic goitre Even more important, however, was the finding that an iodine level which in a soft water may be adequate to prevent goitre may be insufficient where the water is hard. This explains why in Scotland, where the waters are mainly soft, goitre appears at a lower level of iodine intake and is much less prevalent than in England, where the waters are mainly hard

Although goitre is not a common disease in Scotland there are nevertheless some areas where it is prone to occur, namely, in the Southern Uplands and in parts of Inverness-shire. At one time the affected region in the south extended over the greater part of Roxburghshire, the west of

Without doubt the prevalence of goitre in England has considerably diminished over the past hundred years in consequence of rising standards of public hygiene, better food and improved water-supplies; but the disease has never been entirely extinguished and has always continued to disturb the minds of research groups and organizations anxious to improve the *physique and health of the people*. *In the year 1936*, in the County of Somerset, goitre rates of 36% were still the rule among schoolgirls living in the neighbourhood of Taunton, Yeovil and Wells;[894] and in 1940 urgent attention was being drawn in the medical press to the high incidence of goitre persisting throughout South Wales.[844]

The war of 1939-45 brought the subject into a new prominence because of reports that thyroid enlargement was increasing in areas cut off from supplies of sea-fish. It was also noticed that the condition was unusually common among young women drafted into factories for war work. The Medical Research Council of Great Britain thereupon appointed a committee to consider these observations and to carry out special surveys of certain sections of the population in several counties of England and in two in Scotland. Among the committee's findings were established goitre in 50% of adult women at Hook Norton, Oxfordshire, thyroid enlargement in 43% of girls at Sherborne in Dorset, in 26% of boys and girls at Okehampton in Devonshire; and in 21% of girls at St Albans, Hertfordshire. By contrast, only 2% of children showed thyroid enlargement at Maldon in Essex where the drinking-water is rich in iodine.[871]

In short, the areas in which official surveys have located evidence of iodine deficiency in England are the same today as they were 50 or 100 years ago. At the time of their investigation (1944) the Goitre Subcommittee of the Medical Research Council estimated that in England and Wales there were some 500 000 cases of thyroid enlargement in persons of ages 5 to 20 years inclusive.[867] There is no reason to suppose that this figure is any less today, 12 years later; indeed, the following comparatively recent reports suggest the very opposite. Lisney,[881] County Medical Officer of Health, Dorset, refers to a surprising increase in thyroid enlargement coupled with increased lassitude and anaemia among women seen at the Dorchester ante-natal clinic in 1949 compared with previous years. Similarly, Simpson[881] reports thyroid enlargement linked with real ill-health, lassitude and catarrh among expectant mothers attending her ante-natal clinics in the Isle of Wight during 1951. Cooke[841] also describes a symptom-complex among women in West Hartlepool which responds to thyroid medication and is believed to be analogous to, if not identical with, the Roberton syndrome commonly met with in Christchurch, New Zealand. *This involves lassitude, coldness, and hair changes following pregnancy, and is regarded as a* [illegible] associated with endemic goitre. Hoey[851] [illegible] Monmouthshire, [illegible] ommends the

near the sea coast. They extend from Waterfoot near Cushendall in the north, to Derryclone in the extreme south of the County and are bounded on the north by the Atlantic Ocean and the North Channel, on the east by Belfast Lough, on the south by the city of Belfast and the river Laggan, on the west by Lough Neagh, and on the north-west by the Ballymena region of the County. The type of country varies considerably On the north-east is a coastline of steep escarpments rising from the sea, inland a great plateau slopes down to a low-lying area on the west covered by flat bog or deposits of glacial clays and gravels.

Compared with other countries, the average goitre rate in Northern Ireland is not high. In every 1000 children examined, Erskine found 39 cases, of which 26 were in girls and 13 in boys She saw more thyroid enlargement in rural than in urban schools and seldom found a case among sea-coast communities Although the over-all rate averaged only 3 9%, there were some individual schools on the west plateau and in the valleys sloping towards Lough Neagh where the rate reached anything from 9% to 25%

Faulty diet, iodine deficiency, bad hygiene and poor housing are the causes of goitre in County Antrim, according to Erskine Focal and general infections are commoner in goitrous than in normal children; and the adverse effect which the condition has on the health of women during pregnancy and at childbirth is particularly noticeable

Ireland

The general impressions of those competent to judge are that goitre is obviously much commoner in Ireland than in England The area of highest endemicity is the South Riding of County Tipperary, but the disease is also known in County Dublin, County Wicklow, County Meath, and in Kilkenny [910] (also I Brady and T. Stallard—personal communications, 1955) Cases have been recorded in an orphanage in Sligo (M Kirby—personal communication, 1950) and there is a slight incidence in Counties Leix and Mayo Goitre is said to be unknown in Galway and Kerry [911]

The high prevalence in South Tipperary has been the subject of study by the Medical Research Council of Ireland over a period of years, and the results of their investigations are to be found in papers by O'Shea,[911] Naughten,[908] and O'Donovan [910] Data (see Table X) were accumulated from clinical examination of schoolchildren and chemical determination of the iodine content of the local dietary, soils and waters, not only in South Tipperary but, for comparison, in the non-goitrous sea-coast village of Spiddal in Galway, and in Port Laoighise (Maryborough) and Claremorris, two localities of intermediate goitre incidence

These data show clearly how goitre is most prevalent where there is least iodine in the locally produced foods—milk, soda-bread and potatoes. The outstandingly high iodine content of soil and water in the coastal

Berwickshire, the upper parts of Selkirk and Peebles, the northern districts of Lanarkshire, the eastern side of Ayrshire, the whole of Dumfriesshire and Kirkcudbrightshire, and the eastern parishes of Wigtownshire.[900] Today, goitre has largely disappeared from these counties with the exception perhaps of Dumfriesshire, where the valleys of the rivers Esk, Annan and Nith remain distinctly suspect areas The rates of thyroid enlargement found among boys and girls in the 1948 survey of the Medical Research Council were: 19% at Kirkconnel in upper Nithsdale,[a] 20% at Langholm, 23% in the Burgh of Lockerbie, and 17% in the Burgh of Dumfries.

In Inverness-shire a considerable amount of thyroid enlargement has been found among schoolchildren at Fort William, at Kingussie, in the Burgh of Inverness itself, and in Glen Urquhart, where the rates were particularly high, 35% in boys and 47% in girls.[871]

Elsewhere in Scotland goitre is of little account nowadays, but to complete the record it should be mentioned that in earlier times there were goitre centres in Perthshire,[896, 898, 899] in the Isle of Arran,[896] around Wishaw,[903] in the valleys of the western tributaries of the Clyde, especially in the coalmining district of Larkhall,[898] and in and near Fauldhouse midway between Edinburgh and Glasgow on the east side of the Forth-Clyde watershed [901] Goitre is also said to have occurred at one time on the east coast of Fifeshire.[898]

A fairly recent study has been made by Keddie [895] of the distribution of congenital deaf-mutism in Scotland He states that 928 congenital deaf-mutes attended schools for the deaf in Scotland during the 20 years 1924-44, but the records of the districts from which these children came reveal nothing to suggest that deaf-mutism is invariably confined to the goitre areas.

Northern Ireland

During the course of routine medical examination of people from Northern Ireland applying for visas to enter the USA in 1929-30, Olesen & Neal [906] found a surprising amount of simple goitre among individuals coming from all parts of the six counties of Ulster

In all, they examined 4648 males and 3992 females ranging in age from a few weeks to more than 80 years. The rate of indisputable thyroid enlargement among the males was 11.8% and among the females 27.4%. In both sexes the greatest amount of goitre was found between the ages of 15 and 24 years, the percentage being highest (33 1) in girls of 15 to 19 years

More recent investigations have been made by Erskine,[904, 905] who determined the goitre rate in children attending public elementary schools in the south of County Antrim. Here, the goitre areas are typical rural districts with some small towns and villages situated on the main roads and

[a] Long ago Mitchell [902] gave the disease the local name of "Nithsdale neck".

near the sea coast They extend from Waterfoot near Cushendall in the north, to Derryclone in the extreme south of the County and are bounded on the north by the Atlantic Ocean and the North Channel, on the east by Belfast Lough, on the south by the city of Belfast and the river Laggan, on the west by Lough Neagh, and on the north-west by the Ballymena region of the County. The type of country varies considerably On the north-east is a coastline of steep escarpments rising from the sea, inland a great plateau slopes down to a low-lying area on the west covered by flat bog or deposits of glacial clays and gravels.

Compared with other countries, the average goitre rate in Northern Ireland is not high. In every 1000 children examined, Erskine found 39 cases, of which 26 were in girls and 13 in boys. She saw more thyroid enlargement in rural than in urban schools and seldom found a case among sea-coast communities Although the over-all rate averaged only 3 9%, there were some individual schools on the west plateau and in the valleys sloping towards Lough Neagh where the rate reached anything from 9% to 25%

Faulty diet, iodine deficiency, bad hygiene and poor housing are the causes of goitre in County Antrim, according to Erskine. Focal and general infections are commoner in goitrous than in normal children; and the adverse effect which the condition has on the health of women during pregnancy and at childbirth is particularly noticeable.

Ireland

The general impressions of those competent to judge are that goitre is obviously much commoner in Ireland than in England. The area of highest endemicity is the South Riding of County Tipperary, but the disease is also known in County Dublin, County Wicklow, County Meath, and in Kilkenny[910] (also I Brady and T. Stallard—personal communications, 1955) Cases have been recorded in an orphanage in Sligo (M. Kirby—personal communication, 1950) and there is a slight incidence in Counties Leix and Mayo Goitre is said to be unknown in Galway and Kerry.[911]

The high prevalence in South Tipperary has been the subject of study by the Medical Research Council of Ireland over a period of years, and the results of their investigations are to be found in papers by O'Shea,[911] Naughten,[908] and O'Donovan.[910] Data (see Table X) were accumulated from clinical examination of schoolchildren and chemical determination of the iodine content of the local dietary, soils and waters, not only in South Tipperary but, for comparison, in the non-goitrous sea-coast village of Spiddal in Galway, and in Port Laoighise (Maryborough) and Claremorris, two localities of intermediate goitre incidence

These data show clearly how goitre is most prevalent where there is least iodine in the locally produced foods—milk, soda-bread and potatoes. The outstandingly high iodine content of soil and water in the coastal

TABLE X RELATION BETWEEN OCCURRENCE OF GOITRE IN SCHOOLCHILDREN AND IODINE CONTENT OF SOILS, FOODS, AND WATER

Place	County	Goitre in children (%)	Iodine content (μg per 100 g) of				
			soils	waters	milk	soda-bread	potatoes
Cloran	Tipperary	65	3 721	1.9	1.0	1.6	0.5
Kilsheelan	,,	70	3 809	0.9	0.9	0.9	0.6
Tipperary town	,,	65	3 071	0.5	1.5	4.7	0.6
Maryborough	Leix	40	3 010	1.7	3.5	12.6	11.7
Claremorris	Mayo	10	5 050	0.4	3.6	10.7	7.0
Spiddal	Galway	0	14 390	20.1	55.6	18.3	5.6

district of Spiddal corresponds with high iodine in the local foods, and entire absence of goitre

There is no law compelling people to use iodized salt in Ireland, but the public health authorities encourage its use throughout the whole country and particularly in the areas where goitre is known to be prevalent.

France

The geographical distribution of goitre in France is the same today as it has been throughout the past century, although during that time the intensity of the disease has much decreased (Mayet;[911-914] Rochaix[918])

The principal zones are: an eastern belt extending along the entire German-Swiss-Italian frontier from northern Alsace to the Alpes-Maritimes on the Mediterranean coast; a south-central zone covering the Auvergne and Massif Central; and a strong but smaller belt along the Pyrenees and Spanish frontier. Isolated from these three main areas are foci in the Departments of Aisne and Orne in the north-west. Excluding the two last-named, the districts of greatest incidence may be conveniently listed thus.

North-eastern Zone

Moselle	Bas-Rhin
Vosges	Haut-Rhin
Haute-Saône	Doubs

South-eastern Zone

Jura	Haute-Savoie
Ain	Savoie
Isère	Hautes-Alpes
Drôme	Basses-Alpes
Vaucluse	Alpes-Maritimes

South-Central Zone

Puy-de-Dôme	Saône-et-Loire
Corrèze	Loire
Cantal	Rhône
Lot	Haute-Loire
Aveyron	Ardèche
Lozère	Gard

Pyrenees Zone

Landes	Haute-Garonne
Basses-Pyrénées	Ariège
Hautes-Pyrenées	Pyrénées-orientales

In the eastern zone the heaviest intensity lies in Savoy, where the Tarentaise and Maurienne ranges are intersected by many goitrous valleys. Bérard & Dunet [918] regard water as the essential etiological agency in this area and they point to the existence of "conscripts' springs", where recruits used to go to drink the water in order to develop neck swelling and so escape military service They recall, too, the boarding-school at St. Jean-de-Maurienne where the pupils developed goitres during term but lost them when on holiday out of this area, only to develop them again on returning to school. "Holiday goitre" also develops rapidly in individuals from other parts of the country who choose to spend their vacation in these goitrogenic districts To the south, goitre persists in the valleys of the Maritime Alps, more particularly along the rivers Vésubie and Bevera (Marot [939])

North of the Savoy mountains the endemic stream follows a course along the Jura and Vosges whence it swings to the north-west over the Moselle country and through the Ardennes into the northern Paris plain In Alsace the high ground on either side of the Rhine is affected, but the valley between, especially in the neighbourhood of Strasbourg, is goitre-free (Rhein [917])

Of the south-central area covering the Auvergne mountains and extending eastward to the Cevennes and westward to the plain of Aquitaine, there is little to be said except that compared with former times the intensity of the endemic here has greatly decreased in recent years (Berard & Dunet [918]) A series of fairly recent papers by Faugère, Vichnevsky, Laroche, Trémolières and Derache define the present goitre position in the Departments of Corrèze and Lot, which lie in this general area [927, 937, 938, 951, 952] In both these departments goitre rates of 40% to 50% are to be found among schoolchildren of ages between 7 and 18 years.

In the Pyrenees, also, goitre is on the wane according to Rochaix.[948] It has not, however, completely disappeared and what seem to be almost permanent foci still exist in the canton of Luz-Saint-Sauveur, in the valley of the Adour south of Bagnères-de-Bigorre, and in the valleys of the Neste and the Aure (Gleizes & Boy; [930, 931] Marot [939])

Since the intensity of goitre is automatically diminishing with improved conditions of sanitation, and especially of water-supply and nutrition,

preventive measures as practised in other countries have never been considered necessary by public health authorities in France.

Records of goitre among domestic animals are occasionally met with in French veterinary literature. As long ago as 1862 Baillarger[916, 917] described occurrences among mules, horses and dogs in the mountainous eastern regions of the country. More recently (1940), Jacob[933] writes of thyroid disease of hyperthyroid type in foals born in the Breton coastal region north of Brest.

Goitre is not considered to be endemic in Corsica; nevertheless, cases are by no means infrequent in upland villages (Marot[939]).

PART II—AFRICA, ASIA AND OCEANIA

Africa

Isidor Greenwald,[956] the well-known goitre historian, has accumulated what he regards as compelling evidence that goitre, now endemic throughout most of Africa, was unknown in ancient Egypt or in Roman North Africa and, indeed, did not originate anywhere on the African continent until the nineteenth or even the twentieth century.

Nevertheless, there are several early accounts of its existence. Johannes Leo[955] (c. 1494-1552), usually known as Leo Africanus, an Italian of noble Moorish stock and long ranked as the best authority on Mohammedan Africa, records in his *Descrittione dell'Affrica* having seen goitre during his travels (1513-15) through Morocco and the Sahara. This account has been supplemented by a number of later observations which confirm that in North Africa goitre has long been endemic on the slopes and in the valleys of the Atlas Mountains, in Spanish Morocco, and in the Kabylia Mountains in Algeria.

When making his way from the Gambia to the upper waters of the Niger in 1795-96, Mungo Park[960] saw goitre among the native peoples in the Bambuk country and at Segu-Sikoro in the direction of Timbuktu. The first European to reach Timbuktu from Tripoli, A. G. Laing,[958] also mentions goitre in the narrative of his West African journeys (1822) when endeavouring to reach the source of the Niger through the interior of Sierra Leone.

The histological and other characteristics of goitres found among North African immigrants in the Lyons region of France are described in detail by Guinet & Berger.[957]

Algeria

Some of the goitrous localities in eastern Algeria are mapped in a short paper by Sergent[960] published in 1912. He refers to the calcareous nature of the terrain and mentions the regional names given to the disease—

namely, *Handjoura* (Arabic); *Hazzouza* at Thaourirth-naith-gana; *Aghbal* at El-Kseur; *Arkoum* at Tizi-Ouzou; and *Akerkour* at Lafayette.

The fullest and most recent studies are those in 1955 by Vergoz, Boulard & Bernard,[962] and in 1959 by Vergoz & Sicard.[963] They have mapped the endemic area and found it much more extensive than that traced by Sergent in 1912. It seems that the most seriously affected area is the Department of Constantine on the eastern side of the country where the disease is found throughout practically the whole of Little Kabylia from the interior to the sea coast. Goitre centres particularly noticeable in this zone are Collo, Philippeville, El Milia, Taher, Djidjelli, Akbou, La Soummam, Bougie, Guergour, Takitount and Oued Amizour.

The goitre belt continues westwards into Grand Kabylia in the Department of Algiers where comparatively high rates are seen at Tigzirt, Tizi-Ouzou, Michelet, Boghni, Dra-el-Mizan, Palestro, Ménerville, le Fondouk, Rovigo, and Souma This section of the endemic terminates at Blida, just south of Algiers. The city of Algiers itself is immune. Farther to the west there are one or two places on the coast, notably Gouraya and Montenotte, where the prevalence, although lower than in Kabylia, is still disquietingly high

Oran, to the west of the country, is the least goitrous of the three main northern divisions of Algeria The only place where the disease has been noted up to the present is the neighbourhood of Nedroma, which lies near the Moroccan border just south of Nemours

The inquiry by Vergoz, Boulard & Bernard took account of about 40 000 persons—schoolchildren, military recruits, hospital patients and others—of whom 4500 had goitres This over-all rate of approximately 10% rose markedly in certain groups and in certain places Thus, at Takitount in the Department of Constantine, 189 children out of 200 (94 5%) were found to be goitrous, at Souma 65% and at Cap Aokas 61% of children were victims. Women were more intensely affected than men, in an area of high endemicity the figures were 71% for women and 23% for men Cretinism appears to be rare in Algeria, and among the 40 000 people examined there was not a single case of deaf-mutism.

Vergoz and his colleagues make a strong plea for the introduction of iodized salt in Algeria They do this from general economic and humanitarian considerations rather than because they think the goitre scourge in Algeria is exceptionally severe; in fact, goitre is much less intense there than in many other countries They remind us that although goitre may not kill and although its lighter incidences may not seriously affect the behaviour of the subjects (mildly goitrous children are able to pursue their studies and adults are able to marry and have children) it is nevertheless a degenerative social malady from which greater evils may develop and involve unnecessary charges on the medical services of the state. The charge against public funds for goitre operations in Algeria has been

preventive measures as practised in other countries have never been considered necessary by public health authorities in France.

Records of goitre among domestic animals are occasionally met with in French veterinary literature. As long ago as 1862 Baillarger[916, 917] described occurrences among mules, horses and dogs in the mountainous eastern regions of the country. More recently (1940), Jacob[933] writes of thyroid disease of hyperthyroid type in foals born in the Breton coastal region north of Brest.

Goitre is not considered to be endemic in Corsica; nevertheless, cases are by no means infrequent in upland villages (Marot[939]).

PART II—AFRICA, ASIA AND OCEANIA

Africa

Isidor Greenwald,[956] the well-known goitre historian, has accumulated what he regards as compelling evidence that goitre, now endemic throughout most of Africa, was unknown in ancient Egypt or in Roman North Africa and, indeed, did not originate anywhere on the African continent until the nineteenth or even the twentieth century.

Nevertheless, there are several early accounts of its existence. Johannes Leo[985] (c. 1494-1552), usually known as Leo Africanus, an Italian of noble Moorish stock and long ranked as the best authority on Mohammedan Africa, records in his *Descrittione dell'Affrica* having seen goitre during his travels (1513-15) through Morocco and the Sahara. This account has been supplemented by a number of later observations which confirm that in North Africa goitre has long been endemic on the slopes and in the valleys of the Atlas Mountains, in Spanish Morocco, and in the Kabylia Mountains in Algeria.

When making his way from the Gambia to the upper waters of the Niger in 1795-96, Mungo Park[980] saw goitre among the native peoples in the Bambuk country and at Segu-Sikoro in the direction of Timbuktu. The first European to reach Timbuktu from Tripoli, A. G. Laing,[984] also mentions goitre in the narrative of his West African journeys (1822) when endeavouring to reach the source of the Niger through the interior of Sierra Leone.

The histological and other characteristics of goitres found among North African immigrants in the Lyons region of France are described in detail by Guinet & Berger.[957]

Algeria

Some of the goitrous localities in eastern Algeria are mapped in a short paper by Sergent[960] published in 1912. He refers to the calcareous nature of the terrain and mentions the regional names given to the disease—

estimated by Vergoz & Sicard.[963] Hospitalization and surgical treatment of a single case costs 180 000 French francs The hospital of Mustapha alone deals with 150 goitre operations annually, thereby incurring a total expense of 27 million francs Similar costs apply in many other Algerian hospitals operating in the endemic zone. These facts should be faced and preventive measures applied.

The iodine contents of drinking-waters from a non-goitrous locality and from two widely separated goitrous localities in Algeria are compared by Vergoz, Boulard & Bernard[962] The figures have an obvious significance:

	μg of iodine per litre
Algiers (no goitre)	2 0
Souma (goitrous)	0 7
Cap Aokas (goitrous)	0 2

These authors also state that salt supplied for domestic consumption in Algeria, of whatever origin, has a very low iodine content.

Morocco

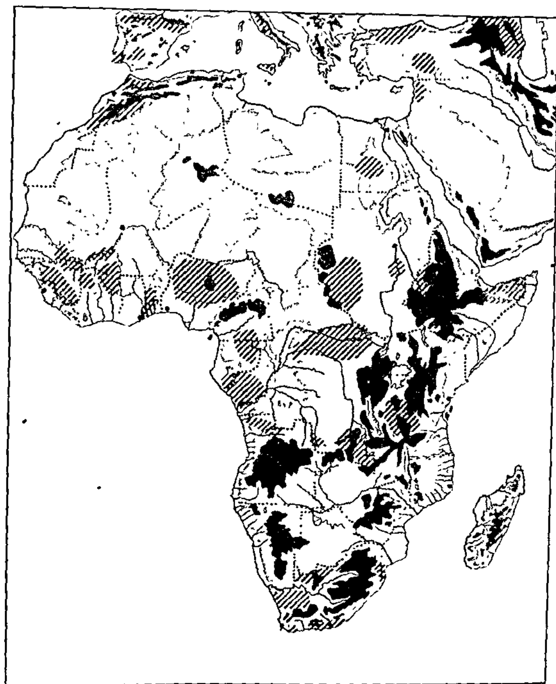
In former Spanish Morocco goitre is called "*Hansla*" by the local people, and endemic centres are to be found scattered here and there along the Rif mountain chain Two of these have been studied in some detail—the *kabila* of Beni Jaled by Manuel Amaro[958] and the *kabila* of Beni Ahamed by Alonso Romeo[964]

The *kabila* of Beni Jaled consists of 72 hamlets with a total of 14 200 inhabitants The district lies in the mountains almost at the centre of the country and through it runs the main highroad connecting the towns of Melilla in the east and Tetuan in the west. Goitre occurs in only four of the 72 hamlets in the *kabila*—namely, Achedad, Ifartan, Takasbut and Taska Out of a total of 300 persons in these four centres taken together, Manuel Amaro found 18 cases of simple goitre, 2 cretins, 2 deaf-mutes, and 1 case of Graves' disease. In each village the affected persons were near relatives all deriving their supplies of drinking-water from the same springs Large quantities of turnips are eaten by these people, indeed, turnips constitute a staple food Manuel Amaro believes this to be a causal factor but thinks also that the district is poor in iodine owing to its altitude and the mountain barriers which shelter it from the sea The prevailing wind is from the desert south

Beni Ahamed, the second district in which a goitre survey has been made, adjoins Beni Jaled on the west Maximum intensity in the zone occurs in the townships of Dar Gaba, Tafsa, Bazet and Kelala Alonso Romeo[964] made a careful clinical examination of 91 cases drawn from 19 townships, and among these he diagnosed hypothyroidism, hyperthyroidism and one case of cretinism.

The endemic area covering the centre of former Spanish Morocco extends southwards into the north of former French Morocco, where,

FIG 5 AFRICA



The red hatching indicates the areas where endemic goitre has been found.

ing for its promoters and for the reviewer than that conducted by the medical officers of the Government Public Health Service in French West Africa under the impetus and direction of Dr Léon Pales.[971 977]

The former Federation of French West Africa embraced the following eight separate territories Mauritania, French Sudan, Upper Volta, Niger, Senegal, French Guinea, Ivory Coast and Dahomey; it covered an area of more than 1 800 000 square miles (4 600 000 km^2), nearly nine times that of continental France, and had a population of about 16 000 000 During the year 1948 the medical administration examined 3 162 039 people, of whom 153 591 were found to be goitrous, that is, 4 86%. At that time Pales[971, 974] concluded from these statistics that there were probably not less than 700 000 sufferers from goitre in all French West Africa

A further investigation was made in 1950 to fill gaps left in the 1948 inquiry and to complete as far as possible the detailed map of distribution The number of Africans examined has now risen to 4 449 040, of whom 371 205, or 8 3%, were found to be suffering from endemic goitre If this new knowledge be accepted as the basis of a general estimate, it will be seen that rather more than 1 300 000 people are afflicted with goitre in this area and that Pales' earlier figure of 700 000 was an underestimate[976]

Excellent maps prepared by Pales & Tassin de Saint Péreuse on a scale of 1: 2 000 000 and printed in five colour gradations from yellow to dark-brown show the distribution and varying intensity of the endemic in French West Africa and also the names of the tribal races occupying the affected locations[972, 975, 976] Looking across the map from west to east and south-east, the following areas stand out as the most goitrous

Senegal

Rates of 14% to 40% are common in the cantons in low-lying east Casamance on the banks of the Songrougrou and Casamance rivers just south of the Gambia High rates are also found around Dialakoto on the upper waters of the Gambia river

Guinea

There are centres of high prevalence (from 12% to 30%) throughout the Fouta Djallon mountain region, which covers practically the whole of the central part of the territory Farther east, rates of 20%, 40% and 50% occur in some of the cantons around the town of Siguiri To the south of Guinea, where it borders on Liberia and the Ivory Coast, the endemic is severe around Macenta, Beyla and N'Zérekoré

French Sudan and Upper Volta

The goitre area at Siguiri continues eastwards without interruption through the southern part of French Sudan and into the territory of Upper Volta Among strongly affected areas are those adjoining the towns of Bougouni, Ségou and Koutiala in the Sudan, and an extensive region

according to Alonso Romeo, the *kabila* of Beni Zerual is greatly affected. However, there do not appear to be any precise accounts of the nature and distribution of goitre in former French Morocco. During their investigation of endemic fluorosis in the phosphate-mining community at Khouribya, which lies inland about 60 miles south-east of Casablanca in the direction of the Atlas Mountains, Murray & Wilson [967] found no evidence or record of goitre in this area. The mean iodine content of four samples of water from the supplies used by the Khouribya settlement was 10 μg per litre, a relatively high amount which would probably account for the absence of thyroid disease in this area of endemic fluorosis.

Madeira and Canary Islands

With regard to the islands lying off the north-west African mainland, goitre is said to be rare on Madeira [8] but rather prevalent on Santa Cruz de la Palma, one of the most westerly islands of the Canary group.

Hernández Feliciano [968, 969] examined 274 cases (13 men and 261 women, the great majority of whom were in middle adult life) from 14 localities and found that the dominant clinical characteristic was one of hyperthyroidism. A map giving the distribution of the 274 cases shows that the disease is not localized but may be found all round the island at widely separated places.

Santa Cruz	86	Tazacorte	30
Breña Alta	8	Tijarafe	2
Breña Baja	4	Puntagorda	5
Mazo	32	Garafía	8
Fuencaliente	1	Barlovento	2
El Paso	13	Puntallana	7
Los Llanos	54	San Andrés	22

Later, he extended his survey to 1104 schoolchildren among whom he found goitre rates of 46.3% in 575 girls and 35.5% in 529 boys.[969]

La Palma is a mountainous island of underlying basaltic structure covered by a thick cap of porous volcanic rock and profusely encrusted with lava, tuff, and banks of sand. The iodine content of the drinking-water, derived chiefly from springs, is exceedingly low, values for samples drawn from nine different localities ranged from 0.11 μg to 0.87 μg per litre, with an average of 0.27 μg per litre. Hernández Feliciano stresses the need for prophylaxis by means of iodized salt.

His study is impressive refutation of the common belief that coastal areas and sea-girt islands are goitre-free.

French West Africa [a]

Of all national goitre surveys none has been bolder in conception, vaster in area, more exacting for the surveyors, and in its results more satisfy-

[a] At the time when the survey described under this heading was conducted, French West Africa was still a political entity.

confer goitre immunity on the peoples inhabiting that particular zone or any zone to which Sahara-produced mineral salt becomes available in the natural course of trade. The fact is, however, that the Sahara salt trade-routes have never penetrated much below the 14th parallel[875] Peoples long established south of that line have for the most part been dependent on vegetable salts that are rich in potassium but may contain little iodine, or indeed, as Pales postulates, may possess a subtle goitrogenic agent as yet unidentified. Inquiries to settle these unanswered questions are proceeding.

In the territories of former French West Africa goitre is about twice as prevalent in women as in men, it is more frequent in adults than in children According to Denoix,[876] whose investigations apply principally to the Upper Volta, the age of greatest frequency extends from 10 to 30 years, with a maximum towards the 15th year, that is to say, about the period of puberty. The largest goitres are seen in old women It cannot be stated with certainty whether diffuse parenchymatous goitres or nodular goitres are the more prevalent, but it is probable that the diffuse type is the commoner Cases of hyperthyroidism are exceptional, and in the statistics cancer of the thyroid is very rarely noted

Goitrogenic cruciferous plants, more particularly the genus *Brassica* (cabbages, turnips, kale, etc), do not figure in the native dietary Indeed, the soils of this region of Africa are of a type far from being favoured by the Cruciferae. Consequently, these are few in number and variety, and, oddly enough, the ones that do occur are found mostly in zones free from goitre.

Prophylactic trials with iodized salt are in active progress and have already given highly promising results, especially at Macenta in Guinea just north of the Liberian border.[877] Pales hopes that these first demonstrations of the efficacy of iodine as a goitre preventive are but the prelude to the systematic iodization and distribution of commercial marine salt extracted in the salt works of the Sine Saloum at Koalack, in Senegal, where the present annual production amounts to 50 000 tons and could be increased without any difficulty Various grades of salt marketed in jute bags from the Koalack factory, and fortified with iodide and iodate at two different levels, have been subjected to storage and transportation tests[879] Coarse salt fortified with iodate is the most satisfactory, inasmuch as iodate does not migrate to the sides and bottom of the bag. Even so, the problem of iodine loss has not yet been finally solved; more than half the iodate in coarse salt disappears within 3 months of storage under inland climatic conditions

Besides spreading over extensive tracts of country in former French West Africa, the goitre belt in this part of Africa also extends into the territories of Gambia, Sierra Leone, Ghana (formerly the Gold Coast) and Nigeria, it continues southwards through Cameroun into the hilly districts of northern Angola A map showing the distribution of endemic goitre in

encircling the town of Dedougou north of Bobo Dioulasso in Upper Volta The most northerly focus in this general area, and indeed one of the most severe in all French West Africa, lies near Bandiagara about 200 miles due south of Timbuktu Here, eight communities register rates of 40% to 73%.

Ivory Coast

The principal goitre centre in this territory lies in the mountainous region of Man. It forms part of the Beyla and N'Zérékoré belt in southern Guinea and shows rates of anything from 10% to more than 40%. Another prominent focus lies to the east-centre of the country immediately north of Katiola 200 miles from the sea, where rates of 31% and 42% have been recorded in the cantons of Fondébougou and Kembigué, respectively.

Dahomey

This narrow strip of territory in the south-east is not so seriously affected as some of the other territories that made up the Federation Nevertheless, there are centres of goitre in the north around Natitiagou and Kandi, and also on the right bank of the Niger opposite the Canton of Gaya.

Viewing former French West Africa as a whole, there would appear to be more goitre in mountainous regions than on the plains But prevalence has not necessarily any connexion with altitude; thoroughly investigated villages, in which a very high proportion of the inhabitants were examined, have shown rates of 30%, 40%, 50% or even more, whether situated in mountainous country or on the plains, in savanna or in the forest Two facts, however, may be regarded as axiomatic: goitre is extremely rare on the Atlantic sea-coast and is likewise extremely rare in the regions of the Sahara Indeed, in this part of Africa goitre is practically non-existent north of the 14th parallel, a line which constitutes an almost rigid east-west barrier between the goitrous and non-goitrous zones The territories of both Mauritania and Niger lie north of this parallel; almost no goitre is found in either.

An arresting explanation is advanced by Pales [971, 974] for this remarkable phenomenon of disease-geography. For the most part, the highly endemic zones are sited upon soil foundations of granito-gneiss—a fact confirmed by Wilson in her later survey of Sierra Leone.[988] Pales, however, does not pay so much regard to this immutable geological consideration as to the fact that in the area covered by his survey, the greater part of which lies to the south of the 14th parallel, the goitrous terrain is precisely the area in which the native peoples are dependent for their supplies of cooking and seasoning salt on " pot-ash " derived from the incineration of local plant foods, and are by reason of economic and transportation difficulties precluded from access to natural sodium chloride derived from sea-water by solar evaporation at coastal centres or from the rich salt-producing areas in the south Sahara.[971, 974]

There is little need, Pales says, to suppose a one-time sea in the Sahara to explain the possible presence in the Sahara salts of sufficient iodine to

showed that the affected areas coincide with the distribution of granitic rocks of pre-Cambrian geological age, and correlated the prevalence of the malady with low iodine content of drinking-water In her paper to the same Society, she makes the following comments "There is thus a belt of endemic goitre from Senegal to Angola which deserves the attention of administrators and clinicians in order that appropriate remedial measures may be instituted The time [in Sierra Leone] is very favourable for the introduction of iodized salt which is the easiest method of dealing with goitre prophylaxis"

Both Blacklock's observations and those by Wilson a generation later show that goitre is absent in the low-lying western parts of Sierra Leone towards the coast; these goitre-free areas are situated on comparatively modern geological formations overlying earlier rocks In the upland eastern section of the country the endemic affects the Mende, Kissi and Kono peoples dwelling in the Kenema, Kailahun and Kono districts of the South-Eastern Province. Among Kono men and women a rate of 56% was noted by Wilson; the thyroid gland was frequently much enlarged, multinodular and cystic, and obvious goitre was sometimes present in young children, but no case of congenital goitre was seen Farther north, the disease occurs among the Koranko living at the base of the Loma Mountains and in the Koinadugu district of the Northern Province where a rate of 71% has been recorded by McIntyre [987] in Bendugu village

On a route from the south to the north of the goitre areas a traveller would pass through the following places of high incidence—Jiama, Paya, Kaiyima and Yaiya in the Kono country, and Saywaia, Kruto, Banda-karafaia, Kimadugu, Bendugu, Kaballa and Dankiwalli in the Koranko country. These villages all lie at the head-waters of the Sewa, Bagwe and Rokel rivers on the watershed between Sierra Leone and the sources of the Niger in Guinea

As already mentioned, the areas of endemic goitre in Sierra Leone are associated with pre-Cambrian granite rocks which have become altered by intensive weathering under tropical conditions It would appear that the chief factor influencing goitre distribution is that these rocks have gradually been deprived of iodine by leaching and that, in consequence, the waters issuing therefrom have an exceedingly low iodine content. Wilson and her colleagues [988] give the following figures:

	Goitre rate (%)	*Iodine content of water (µg per litre)*
Highlands (to the east)		
Koinadugu (Koranko)	42 9-71 0	<1 0
Kono . . .	55 9	<1 0
Kenema and Kailahun .	19 0-24 7	<1 0
Lowlands (to the west)		
Kambia—Port Loko area .	no goitre	1 0-2 8
Moyamba—Bo area . .	no goitre	4 3

relation to the geological occurrence of pre-Cambrian rocks throughout the whole of West Africa is given by Wilson et al.[988]

Gambia

Writers on goitre in this part of the world are wont to say that the explorer Mungo Park [980] saw goitrous people in Gambia when making his way to the upper waters of the Niger in 1795-96. He mentions having seen cases in the Bambuk country and in the neighbourhood of Segu; but these places lie hundreds of miles beyond Gambia to the east, and it is not certain that Park saw goitre actually in Gambia itself.

That the disease does occur there, however, has been recorded by Todd [999] and more recently by M. P Hutchinson (personal communication to D C Wilson,[988] 1952) The affected area lies in the upper river district to the east where the pre-Cambrian granite formations begin, and is obviously linked up with the Senegal endemic in the same region It would not be surprising, either, if goitre were found in the centre of the country in the neighbourhood of Georgetown because, in Senegal, both north and south of the Gambia river at this point, goitre is known to occur (see page 119)

Sierra Leone

" Ballansama is a man of the middle size, of a jolly appearance, both in person and expression, though a little disfigured by a large wen on his throat, which appears a disease very common to the Kooránkos " That is how Laing [986] described the King of Northern Koranko whom he met in 1822 when travelling through the interior of Sierra Leone to explore the sources of the Niger The Koranko country is goitrous today In fact, Sierra Leone provides an excellent example of how, in spite of energetic studies at widely separated intervals of time and strong recommendations for iodine prophylaxis on more than one occasion, only desultory efforts to remedy the situation have as yet been made and goitre still persists

During December 1923 and the early part of 1924, Blacklock [981, 982] and his wife made a strenuous three-month tour into the hilly regions of the east and north through the tribal country of the Kono and Koranko, where they found goitrous people in considerable numbers Their findings were fully discussed at a meeting of the Royal Society of Tropical Medicine in 1925, when Blacklock concluded his address with these words: "I am particularly anxious to ascertain what is the experience of members of this Society in regard to the administration of iodine to populations, because if the risks are indeed negligible, it is our duty to take steps to deal with the problem of goitre in our tropical possessions as soon as possible."

Almost exactly thirty years later, Wilson [988] traversed more or less the same route, found high percentages of goitre where Blacklock found them,

Broadly speaking, the geological layout of Nigeria consists of three upland areas of pre-Cambrian granite—one in the north, one in the south-west, and one in the south-east—separated from each other by belts of marine sediment lying roughly in the form of a letter Y across and down the middle of the country. These belts follow the great valleys of the rivers Niger and Benue, the one flowing from the north-west and the other from the north-east along the converging arms of the Y to meet at Lokoja and thence sweep southwards to the sea as one

The goitrous areas invariably lie on the granites of the pre-Cambrian complex, or in districts dependent on waters derived from these rocks Goitre is absent on the marine sediments of the Niger-Benue river basins. The central plateau in the cup of the Y, an area studied by Wilson more intensively than any other, is of special interest inasmuch as basaltic and lava flows of Tertiary and Recent Age cover part of the granite. Here, families living or farming on the basalt are free from signs of goitre, they *obtain much larger yields of crops. For example, the Vom section of* the Berom tribe live on granite but farm on basalt and are mostly non-goitrous; but another section of the Beroms, not far away at Forum, live and farm on granite and have many goitrous women among them. Similarly, on the escarpment between Pankshin and Shendam towards the south of Plateau Province, and in the adjoining parts of Bauchi Province, goitre is common among tribes using waters that drain off the granite formations of the Naragota, Shere, Jarowa and Jere hills

Wilson lists the goitre districts of Nigeria as follows

Northern Region	
North-west and south of Sokoto	East of Niger
North of Niger	South and east of Zaria
East of Katsina	West and south-east of Bauchi
West of Kano	North and east of Benue
South of Bornu	Many parts of Plateau Province
North-east of Ilorin	East and west of Kabba
Western Region	
North of Oyo	North and west of Ondo
Eastern Region and British Cameroons	
North of Ogoja	Bamenda District and south of Yola
Western part of Mamfe Division	

All these areas of endemic goitre lie on granites of the pre-Cambrian basement complex, or are associated with waters which drain off these rocks The only exception, as explained above, is on the central plateau, where an obvious difference in prevalence and degree of thyroid enlargement (much less, if any at all) was found amongst aboriginal peoples living in granite districts overlain by basaltic lava flows of more recent origin.

The prevalence in relation to the iodine content of the water-supplies in these districts of differing geology is brought out in Table XI (Wilson [997])

Goitre was found to be endemic where the waters contained less than 1.0 μg of iodine per litre, but was not recorded where the iodine content was 2.4 μg per litre or above. Sea-fish, the other important source of dietary iodine, is obtainable by most people near the coast but is rarely eaten in the more distant inland areas where goitre occurs. Another factor which, according to Wilson, may contribute to the causation of goitre in Sierra Leone concerns the intake of vitamin A from red-palm oil. It will be recalled that Haubold [603] found a high prevalence of goitre in mountain villages in Bavaria associated with a low intake of vitamin A and carotene. In Sierra Leone the intake of fats is generally speaking adequate and that of vitamin A from red-palm oil is high. But the availability of red-palm oil depends on oil-palm density, which in the goitre areas of Kono and the adjacent Koinadugu country is not nearly so high as elsewhere, and supplies suffice only for a short season. It is possible that this seasonal scarcity may help to precipitate goitre in places where the iodine content of the diet is already precariously balanced on the borderline between sufficiency and insufficiency.

Ghana

In the extreme north of the Northern Territories of Ghana goitre has been noted by F. C. Rodger (personal communication to D. C. Wilson,[988] 1953) on the banks of the Red Volta and also for 50 miles along the Sissili river, a northern tributary of the Volta. He describes the goitres as "colloid-looking" and, in one place, as being associated with fluorosis. In this same general area goitre has also been observed by B. B. Waddy (personal communication to D. C. Wilson,[983] 1954) near the junction of the Red and White Volta rivers and in the Navrongo and Bawku districts close to the boundary between Ghana and the Republic of the Upper Volta (formerly the Upper Volta Territory of French West Africa).

Nigeria and British Cameroons

When journeying through Nigeria in the early years of this century, Tonkin [994] came across goitre in Gitata, a small pagan village perched high on a rocky ridge, almost exactly in the centre of the country immediately north of Keffi on the trade route between Loko on the river Benue and Zaria some 200 miles northwards. Tonkin estimated that 20% of the village inhabitants were affected, some with very large goitres. He saw no sign of the disease in the valleys on either side of Gitata.

Several later and more or less casual observations have been made from time to time—notably by Denfield,[990] who has vividly portrayed the goitres seen in the Bauchi Plateau in a series of remarkable photographs—but it was not until 1951-53 that Wilson and her colleagues [989, 995, 997] correlated the various scattered pieces of information, added to them, and presented a picture of the Nigerian endemic as a whole.

area to the east of Cameroun (formerly French Cameroon) and the other at Koumra, which lies between the rivers Chari and Logone-Pendé about 60 miles west of Fort Archambault.

Cameroun

There is goitre in the Bamum country in the west of Cameroun and also in the mountainous region occupied by the Wandala tribe in the north; but the most seriously affected area lies between the rivers Lom and Kadei in the east of the country This was surveyed in detail by Masseyeff[1001, 1002] in 1953.

The area is formed entirely of primary granitic material of pre-Cambrian age, with the exception of the semi-metamorphic series of schists and quartzites in the valley of the Lom The south is a region of forest, very dense in some places, and the north is to a great extent covered by a savanna of *Imperata cylindrica* The soil is poor and the area is sparsely populated with a total of about 100 000 inhabitants in a density of the order of 1 85 persons to the square kilometre This section of Cameroun is crossed by two great intercolonial travel routes, one running from west to east through Bertoua and Batouri, and the other from Bertoua to the north through Bétaré-Oya and Garoua-Boulaye. It is in these places and in other villages and settlements along the two thoroughfares that goitre occurs

Masseyeff investigated five localities: the villages of Garoua-Boulaye and Bétaré-Oya in the savanna region of the north; certain villages, also in the savanna, situated on or near the north-south route from Bétaré-Oya to Bertoua, the villages of Yanda, Kanda and Mbeth in the forest region immediately to the west of Bertoua; the western environs of Batouri where the villages of Bakombo and Ndimbo lie in open forest near the savanna, and some forest villages situated in clearings in the region of Ngélebok. A total of 4397 men, women and children were examined; the results are shown in Table XII

These figures show that the disease is extremely prevalent, especially in women It appears, too, that it is most severe at the boundary between savanna and forest and tends to avoid true savanna and deep forest. All the very dense goitre zones are on granite soils; the endemic diminishes in areas where the soils are derived from gneiss, schists and other metamorphic rocks

Nodular goitres are much less common than diffuse goitres, some of which are of enormous size, " greater in volume than the heads of the individuals bearing them " Consequently, deaths due to tracheal compression are frequent Hyperthyroidism is rarely, if ever, seen Those who know the country well say that the people are particularly lethargic and indolent wherever goitre is most in evidence Every small village has one or two goitrous cretins These pathetic creatures live an almost purely vegetative

TABLE XI RELATION BETWEEN PREVALENCE OF GOITRE AND IODINE CONTENT OF WATER-SUPPLY IN SOME PLACES IN NIGERIA

Place	Source of water	Number of subjects examined	Percentage with goitre	Iodine content of water (µg per litre)
Zagun	Older granite of pre-Cambrian basement complex	162	46	0 6 0 7
Miango	Basaltic lava flows of Tertiary and Recent Age	150	Nil	5 0
Vom	Pre-Cambrian granite, but people farming mainly on basalt	250	3	0 6
Abakaliki	From deep water shaft Marine sediments Niger river basin	301	Nil	92 *

* On lead-zinc mine, probably exceptional

The exact incidence of goitre throughout Nigeria is unknown Among Rukabi families in Zagun village, Wilson found an average rate of 46%, the distribution being 32% in adult men, 72% in adult women, 23% in boys and 25% in girls under 16 years of age Hyperthyroidism is rare, but cretinism and deaf-mutism are frequently seen In Nigeria livestock are moved about over wide areas, and the only recorded occurrence of goitre among animals concerns a herd of pigs belonging to a bacon factory situated in a district where human goitre is prevalent, the condition cleared up following the administration of an iodine supplement

There is no evidence that goitrogenic factors other than iodine-deficient waters are operative in Nigeria The endemic is not confined to regions where vegetable ashes are used as salt, as is the case in former French West Africa (see Pales [971, 973, 974]) Local sources of salt are insufficient for the country's needs, accordingly, imported salt is sold in Nigerian markets The question of making iodized salt the only type imported into Nigeria is being considered by the Federal Medical Department.[993] Already, regulations prohibiting the use of non-iodized salt have been made by Tiv, Nasarawa, Zaria, Idoma, Igala, Donga and Takum Native Authorities in the Northern Region Iodized salt means salt to which has been added potassium iodide in a proportion of not less than one part in fifty thousand

Cameroun and French Equatorial Africa [a]

Two highly interesting zones of endemic goitre have been the subject of study by doctors of the French Colonial Service—one in the Lom-Kadei

[a] At the time when the studies described here were conducted, Cameroun had not become an independent republic and French Equatorial Africa still existed as a political entity

Here, in the heart of the country of the Saras—a beautiful, well-built, easy-going, brave and devoted people—goitre (called locally " *Kûa* " or "*Kanreu*") has long been notorious. Bouilliez, director of trypanosomiasis investigations at Fort Archambault, described and mapped the endemic area in 1916, noting that about 80% of the population were affected[999] His successor, Muraz,[1003 1005] confirmed Bouilliez's observations in 1922, added to them, and published his most recent comments on the goitres of this area in 1943.

Dupont found it exceedingly difficult to establish the exact over-all percentage prevalence of goitre among the Koumra people, but could fix it definitely at 75% among men presenting themselves for medical examination prior to military service. Since, as elsewhere, goitre in Koumra is found more frequently in women than in men and also occurs in children of quite tender age, Dupont concluded that practically the entire Koumra population suffers from the disease. This is in marked contrast to the estimated rate of 2 5% in the Region of Moyen-Chari as a whole, and less than 1% in the Region of Ombella-M'Poko, about 300 miles farther south, where a general survey of 51 villages in the Bangui area was carried out by Nimier at Dupont's request.

Although the Koumra goitres are seen more often in women than in men, Dupont found goitre more prevalent in boys than in girls The goitres in females do not make their first appearance at the time of puberty; they are either earlier or later. During pregnancy the swelling markedly increases in volume but diminishes after the accouchement Some goitres reach an enormous size. The average neck circumference of a well-built non-goitrous adult Sara is 14-15 inches (36-38 cm) in a man and rather less in a woman In goitred people Dupont found circumferences of nearly 23 inches (58 cm) in a woman of 20, and 22 5 inches (57 cm) in a man of 25 years of age Goitrous children had neck circumferences of 14 5-16.5 inches (37-42 cm) and an infant of 18 months with thyroid enlargement had a neck measurement of 11 inches (28 cm)

Cases of goitre in children under 5 or 6 years of age are exceptional, most frequently the goitre becomes manifest about the age of 20 years and in some instances its development may be very slow, extending over 20, 30 or even 35 years These slowly evolving tumours are a common cause of sudden death due to asphyxia; the unfortunate sufferer, apparently in good health on falling asleep, will without warning be seized by suffocation during the night and die rapidly The other usual complications of goitre—hyperthyroidism, myxoedema, cancer of the thyroid—are rare in Koumra.

Bouilliez considered that the origin of goitre in Koumra lay in the parasitic infection very prevalent in that area[999] Muraz[1003 1005] also held the same view, but observed a definite ethnical predisposition inasmuch as the people of the Baguirmian-Hausa colony, who had at that time been living alongside the Sara people for 20 years and had been using the same

TABLE XII PREVALENCE OF GOITRE IN SOME LOCALITIES OF CAMEROUN

Locality	Males		Females	
	number examined	percentage with goitre	number examined	percentage with goitre
Savanna region (north)				
Garoua-Boulaye and Bétaré-Oya	451	29 9	135	50 4
On route from Bétaré-Oya to Bertoua	501	59 3	408	76 0
Forest region (south)				
Environs of Bertoua (to west)	745	54 9	933	72.9
Environs of Batouri (to west)	341	51 9	273	82 4
Region of Ngélébok	382	37 7	228	50 0
Total	2420	48 0	1977	70 7

existence, insensible of their surroundings and unable to do more than eat and sleep In this region, too, goitre is of common occurrence among goats, and hunters report having killed goitrous rabbits.

Masseyeff could prove no definite relationship between the occurrence of goitre and the consumption of any particular food such as groundnuts or maize, although it seemed to him that the zones in which maize is grown and consumed coincide very well with those of high goitre rates The young shoots of the alimentary herb " sissongho " (*Pennisetum purpureum*) are much appreciated by both man and beast in this district and it would be interesting to inquire by laboratory experiment whether this food has any goitrogenic properties

At one time salt made from incinerated vegetable material was extensively used, but it has long been abandoned in favour of imported salt. The prevalence of goitre has not thereby diminished; consequently, the hypothesis advanced by Pales [971, 973, 974] that vegetable salt contains a goitrogenic principle does not appear to Masseyeff to be applicable in Cameroun He advocates the introduction of iodized salt, with potassium iodate as the iodizing agent.

Koumra

On a journey from Algiers across the Sahara and down through French Equatorial Africa by way of Tamanrasset, Agadès, Zinder and Fort Lamy as far as Bengui on the border of the Belgian Congo, Dupont [1000] saw goitres in many places; but nowhere were they so numerous or so massive as in the neighbourhood of Koumra, which lies at the centre of a subdivision of the Region of Moyen-Chari between the rivers Chari and Logone-Pendé not far west of Fort Archambault.

Here, in the heart of the country of the Saras—a beautiful, well-built, easy-going, brave and devoted people—goitre (called locally "*Kâa*" or "*Kanreu*") has long been notorious. Bouilliez, director of trypanosomiasis investigations at Fort Archambault, described and mapped the endemic area in 1916, noting that about 80% of the population were affected.[999] *His successor, Muraz,*[1003 1005] *confirmed Bouilliez's observations* in 1922, added to them, and published his most recent comments on the goitres of this area in 1943

Dupont found it exceedingly difficult to establish the exact over-all percentage prevalence of goitre among the Koumra people, but could fix it definitely at 75% among men presenting themselves for medical examination prior to military service. Since, as elsewhere, goitre in Koumra is found more frequently in women than in men and also occurs in children of quite tender age, Dupont concluded that practically the entire Koumra population suffers from the disease This is in marked contrast to the estimated rate of 2 5% in the Region of Moyen-Chari as a whole, and less than 1% in the Region of Ombella-M'Poko, about 300 miles farther south, where a general survey of 51 villages in the Bangui area was carried out by Nimier at Dupont's request

Although the Koumra goitres are seen more often in women than in men, Dupont found goitre more prevalent in boys than in girls. The goitres in females do not make their first appearance at the time of puberty, they are either earlier or later During pregnancy the swelling markedly increases in volume but diminishes after the accouchement Some goitres reach an enormous size. The average neck circumference of a well-built non-goitrous adult Sara is 14-15 inches (36-38 cm) in a man and rather less in a woman In goitred people Dupont found circumferences of nearly 23 inches (58 cm) in a woman of 20, and 22 5 inches (57 cm) in a man of 25 years of age Goitrous children had neck circumferences of 14 5-16 5 inches (37-42 cm) and an infant of 18 months with thyroid enlargement had a neck measurement of 11 inches (28 cm)

Cases of goitre in children under 5 or 6 years of age are exceptional; most frequently the goitre becomes manifest about the age of 20 years and in some instances its development may be very slow, extending over 20, 30 or even 35 years. These slowly evolving tumours are a common cause of sudden death due to asphyxia, the unfortunate sufferer, apparently in good health on falling asleep, will without warning be seized by suffocation during the night and die rapidly. The other usual complications of goitre—hyperthyroidism, myxoedema, cancer of the thyroid—are rare in Koumra

Bouilliez considered that the origin of goitre in Koumra lay in the parasitic infection very prevalent in that area[999] Muraz[1003 1005] also held the same view, but observed a definite ethnical predisposition inasmuch as the people of the Baguirmian-Hausa colony, who had at that time been living alongside the Sara people for 20 years and had been using the same

drinking-water from deep wells, did not present a single case of thyroid enlargement; they were entirely free from the disease. Dupont,[1000] on the other hand, regards causation as wholly a matter of water-supply. He was struck by the fact that there is very little goitre in towns or villages situated directly on the banks of rivers in the neighbourhood of Koumra. There is none at Goundéré on the river Mandoul only a few miles away. There is practically none at Fort Archambault on the river Chari, all the goitrous persons seen there came from the region of Koumra.

The drinking-water of Koumra is obtained solely from a group of 11 deep wells. One of them, no longer yielding much water but once the main source of the community, has a depth of more than 120 feet (38 m); another, now supplying most of the people, is 92 feet (28 m) deep. Dupont inclines to the theory that goitre is infectious in origin; rivers are pure and undefiled, being sterilized by the intense tropical sun, whereas waters from deep wells, being deprived of the sun's beneficent action, retain all sorts of impurities caused by the infiltration of infected products cast out by the inhabitants, even into the wells, in spite of notices that this is prohibited.

Muraz [1001, 1002] first proposed prophylaxis by iodized salt in 1926, but the scheme broke down through lack of co-operation. Dupont,[1000] writing 15 years later, believes that, for the time being at any rate, the goitre problem in this part of the world can only be attacked by surgery or by the individual administration of tincture of iodine or potassium iodide. The general iodization of the sun-dried salt which comes in slab form into this area, especially from Lake Chad, is, he thinks, impracticable. Worthy of mention *in this context—simply to emphasize local ignorance and futility in these* matters—is the native remedy of tying a piece of twine or a thong of antelope skin tightly around the goitre in the hope of limiting its growth. A similar Nigerian custom is described by Denfield.[990]

The most recent (1958) goitre rates in former French Equatorial Africa, as recorded by Bascoulergue,[998] are shown in Table XIII.

TABLE XIII. GOITRE RATES IN FRENCH EQUATORIAL AFRICA, 1958

Territories	Number examined	Goitrous	%
Chad (13 districts)	578 081	78 096	13.4
Oubangui-Chari (39 districts)	978 328	48 550	4.9
Moyen-Congo (29 districts)	408 266	2 305	0.5
Gabon (9 districts)	200 028	873	0.4
Total	2 164 703	129 824	

In the territory of Moyen-Congo (now Republic of the Congo) the district of Dongou had the highest rate with 10%; in Gabon the highest rate was 7% in north Koula-Moutou; and in the province (now Republic) of Chad the highest rates were found at Koumra, Moissala and Kyabe with 36.4%, 25.9% and 12.7%, respectively. Comparatively high rates were found in the province of Oubangui-Chari (now the Central African Republic) particularly at Bozoum (20.3%), Bakouma (16 5%) and at Bangassou (12.7%)

Angola

The West African goitre belt, which, as already shown, begins in Senegal and extends southwards along the pre-Cambrian foundations of the Gambia through Sierra Leone, the Ivory Coast, Ghana, Dahomey, Nigeria and Cameroon, eventually reaches Angola, where the disease has been noted near the diamond mines in the north-eastern parts of the country by A. Warwick (personal communication to D C. Wilson,[988] 1954)

Goitre is also found in the elevated plains of Benguela which rise eastwards towards Huambo in the west-centre of Angola Here, Leitch[1006] mentions especially one hilly district which is named " Goitre Mountain " owing to the fact that practically all its inhabitants are affected

Just outside the extreme south-east border of Angola runs the narrow Caprivi Strip connecting South-West Africa with Rhodesia and separating Angola from Bechuanaland B T. Squires (personal communication, 1955) reports a high prevalence in the strip and has seen cretinism there Since goitre knows no political boundaries it may be taken for granted that the endemic spills over into Angola at this point (see also page 144, Steyn et al[1065]).

Egypt

More than thirty years ago Dolbey & Omar[1007] drew attention to the fact that up and down the valley of the Nile simple parenchymatous or colloid goitre is extremely common among the fellaheen—the farmers or field labourers of Egypt—who make up about 80% of the total population At that time hyperthyroidism was scarcely ever seen among the fellaheen, but there were increasing and disquieting signs of it among the cosmopolitan inhabitants of the towns and among Egyptians of wealth and leisure who, from considerations of taste or of employment, lived in the larger cities and had adopted European habits and diet.

Recent research by Ghalioungui[1009] has entirely confirmed the frequency of thyroid disease in Egypt. In a series of 892 patients seeking treatment for endocrine disorders of various kinds he found 643 " thyroid cases " (72%) and of these more than half were hyperthyroid In Ghalioungui's view the *general prevalence of thyroid disease in Egypt* must be higher than these

figures indicate because most people suffering from simple uncomplicated goitre do not come for consultation, only those who experience toxic symptoms present themselves

Goitre is said by Dolbey & Omar[1007] to have been known to the ancient Egyptians and to have been depicted on their monuments, reliefs and drawings; but Ghalioungui can find no confirmatory evidence of this in the works of archaeologists and authors who have studied ancient Egyptian civilization from a medical standpoint.[1011] The picture of Cleopatra in Ruffer's *Studies in the Palaeopathology of Egypt* (1921) cannot be considered a portrait, and the slight bulge in the neck region is possibly an exaggeration due to the high-relief technique practised by Egyptian carvers of that epoch. Nor, in a fairly wide experience of old Egyptian monuments and their reproductions does Ghalioungui remember having seen a cretin, a hypothyroid, myxoedematous, or goitrous person represented. However, there is no reason to believe, he says, that goitre did not exist among ancient Egyptians, since the conditions of soil, food and water that prevailed forty centuries ago must have been very much the same as those existing today.

First to mention the endemic as distinct from the sporadic occurrence of goitre in Egypt was Ibrahim,[1012] who found it in the villages of the Dakhla Oasis, which lies 200 miles west of Luxor and 350 miles south of Alexandria. The village with the highest goitre rate was El Qalamun, where 18% of the men had goitre and 3 children out of 35 examined were definite cretins Other villages were less seriously affected, but there was a rate of 6% among adult males at Mut and cases were also seen at El Gedida, and at El Khârga in The Great Oasis to the east of Dakhla It was not possible to examine any women

Further and more up-to-date information about the goitre endemic in the Dakhla Oasis is available in two surveys made by Ghalioungui, the first in 1951 and the second in 1955.[1009 1011] The results of the second survey are summarized in Table XIV

TABLE XIV. PREVALENCE OF GOITRE IN THE DAKHLA OASIS, 1955

Age-group	Mut			El Qalamun			El Rashda			El Gedida			El Moushia		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Under 10 years	34	Nil	Nil	73	18	25%	90	14	15%	45	17	38%	65	9	14%
10-15 "	6	2	33%	15	8	53%	23	11	48%	7	4	57%	1	Nil	Nil
15-20 "	7	5	71%	1	Nil	Nil	—	—	—	—	—	—	1	Nil	Nil
Above 20 "	20	2	10%	38	10	26%	17	1	6%	86	39	45%	13	1	8%
Tota . .	67	9	13%	127	36	28%	130	26	20%	138	60	43%	81	10	12%

A = number of people examined, B = number with goitre; C = percentage with goitre

Goitre is common in all parts of the oasis. The highest over-all rate (43%) is seen in El Gedida and the two lowest in Mut (13%) and El Moushia (12%) The condition most frequently occurs between the ages of 10 and 15 years, and the age-group that seems to suffer least is that over 20 years; this may be partly accounted for, however, by the fact that the young men regularly migrate to the Nile Valley towns when they come of age The general level of intelligence, initiative and activity is very low; defectives were found in greatest number in El Gedida, the village with the highest goitre rate Obvious cretinism and myxoedema are rare

Regarding the cause, Ibrahim [1012] says that, so far as the Dakhla Oasis is concerned, contaminated drinking-water is out of the question, the water comes from artesian wells at a great depth and is comparatively pure. However, it contains large amounts of calcium and magnesium sulfate and Ibrahim regards this as the chief causative factor Ghalioungui [1011] also agrees that in the oasis polluted water can be excluded from consideration. On the basis of iodine analyses he holds that the cause of the Dakhla endemic is, quite simply, the lack of sufficient iodine in the soil, water, local salt, and agricultural products. This situation is aggravated by hard water; the varying calcium, magnesium, manganese and chlorine content of the different wells probably accounts for the different rates at different parts of the oasis Fish are unknown and are regarded as legendary animals. Goitrogenic foods, such as cabbage, do not form part of the diet of the oasis dwellers

In the Nile Valley, on the other hand, polluted water is without doubt the primary goitre-producing agency, in the opinion of Dolbey & Omar [1007] People living in villages situated immediately on the banks of the Nile drink the river water, it is comparatively clean and these riparian villagers do not develop goitre as a rule Thyroid enlargement occurs almost exclusively among people living in villages away from the Nile where the wells and irrigation channels are incredibly polluted. Similarly, Dolbey & Omar found no goitre among the bedouin Arabs who drink from remote desert wells yielding water which is purity itself compared with that from the grossly polluted pools, wells and canals in the villages of the fellaheen

Sudan

At least five centres of endemic goitre have been located in the Sudan (1) on the Nile around Ed Damer in the Northern Province, (2) at Halfayet el Melouk, a small village about 20 miles north of Khartoum; (3) in the Upper Nile Province among the Neur and Shilluk tribes south-west of Malakal, (4) in the mountains of Darfur Province to the extreme west of the country; and (5) in a narrow strip of territory inhabited by the Azande in the south-west

The first and fourth of these endemic areas are of comparatively minor importance The second and third have recently (1956) been studied in

some detail by Ghalioungui et al.[1010, 1013] They examined a total of 809 people, ranging in age from infancy to more than 60 years, and found that 402 of them, or 49.6%, had definitely enlarged thyroid glands. Sixty-five of these subjects (16 goitrous) were seen at Halfayet el Melouk; the remainder were located either in Malakal itself or in villages situated along the Bahr el Zaraf (Giraffe river), Bahr el Jebel (White Nile), and Bahr el Ghazal (Gazelle river) to the west and south-west of Malakal. The particulars are shown in Table XV.

TABLE XV. PREVALENCE OF GOITRE IN TWO ENDEMIC AREAS IN THE SUDAN, 1956

Village	Number of people examined	Number of goitrous people	Percentage with goitre	Iodine content of water (µg per litre)
Halfayet el Melouk	65	16	24	—
Malakal	86	30	34	—
Bantiu	242	149	62	—
Leer	79	27	34	5.7
Fangak	102	34	33	2.4
Wankai	181	116	64	—
Tarnob	45	25	55	0.7
Miscellaneous	9	5	55	—
Total .	809	402	49.6	

The highest rate (64%) was seen in adolescents between 10 and 19 years of age, but there was also a 60% rate among children below 5 years. Water from three localities was examined for iodine content; samples from Tarnob, where the goitre rate is high, had a very low content.

The fifth endemic area in the Sudan covers a tract of country approximately 200 miles long and 60 miles wide, lying roughly on a SE-NW axis just where the Sudan borders on the Central African Republic (former French Equatorial Africa) and the Belgian Congo. It includes such places as Yambio, Naandi and Tambura, and is a region that presents features of unusual interest to the student of goitre. These have been fully described by Woodman.[1014] Throughout the area are found the sources and head-waters of innumerable small streams flowing northward towards the Nile. The soil is predominantly ironstone laterite with acid clay catenas. Limestone is conspicuous by its absence. Sun-eroded areas are liable to become sandy and to have much of the nutritive content of the thin soil layer leached out and carried away by percolating water. Nevertheless, this narrow strip is

known as the " green-belt " because it contains the most fertile soil of the region

The most striking, and most puzzling, characteristic of the endemic is the apparently strict territorial limits within which it is confined. On the east the disease virtually disappears at longitude 29°, proceeding 60 miles to the north where rainfall is slightly less, where the streams increase in size but diminish in number, and where the soil gets poorer, goitre becomes less and less common and soon disappears, the western margin of the endemic ends abruptly on the borders of the Central African Republic where the streams run south-westward from the divide to join the M'Bomou river and eventually the Congo; the same applies to the south, where the streams run towards the Uele and the Congo

Restriction of the endemic to this relatively small strip of 200 miles by 60 miles is hard to explain on ecological grounds. As Woodman[1011] points out, the same kind of terrain, the same tribe and the same conditions of diet exist to the east of longitude 29°, where the endemic stops, as pertain in the heart of the endemic area. Similarly, why is it that only occasional goitres are seen immediately south and west of the watershed where the laterite soils are identical with those of the endemic strip ?

On an average about 3% of the population have goitre and nearly 85% of cases are in women. The condition is commonest between the ages of 13 and 35 years, although there are many cases in girls of ten years and younger, in one instance an infant in arms and a child of three and a half were affected Parenchymatous colloid goitre is the usual type but adenomatous goitres are also seen. Hard nodular thyroids are occasionally met with in patients between 40 and 60 years and are usually becoming malignant Many of the goitres seen in young women involute to comparative normality but a large proportion attain a weight of 4-6 ounces (110-170g); sometimes tumours of 16-20 ounces (450-570 g) are seen. The almost complete absence of true Graves' disease is a feature; in fact, the type of goitre seen in this area is described by Woodman as the least toxic of all known varieties. Cretinism and myxoedema are non-existent.

A presumption that within the endemic area the soils and waters lack sufficient iodine to prevent goitre cannot, in Woodman's view, readily account for all aspects of the endemic in this district. Altitude, climate, soil (as far as it has been investigated by chemists), flora, tribal inhabitants, diet, and incidence of parasitic infection and other diseases continue to be the same outside the affected strip, yet there is no goitre. Can it be, he asks, that the virgin streams, after flowing for 50-60 miles through a leached and sandy terrain, begin to derive iodine from rotting vegetation or other source? Chemical determinations of iodine can alone answer this, and it would seem of the greatest importance to have these carried out on samples of water and soil from both inside and outside the goitrous area before indulging in further speculation.

Woodman concludes: " It is hoped to make iodized salt available in all the shops of the endemic area It would be ideal if this could be the only salt on sale "

Ethiopia and Eritrea

The high plateau of Ethiopia figures prominently as a focus of endemic goitre in north-east Africa In 1904 Singer [1020] made a journey from Khartoum up the White Nile and along the Sobat and Baro rivers into Ethiopia, whence he ascended the plateau and traversed *the whole country from west* to east as far as Djibouti in French Somaliland

People with goitre were met with throughout the entire plateau, more commonly on the west side than on the east, but none was seen at the point of entry into Ethiopia, namely, in the flat country below the plateau where the Sobat and Baro debouch from Ethiopia into the Sudan. This confirms the observations of Balfour (see Blacklock [982]), who saw no goitre when travelling on the Pibor river, a tributary of the Sobat, in 1903.

Singer's cases were usually enormous goitres of the parenchymatous type, but adenomatous and other forms were encountered, and Graves' disease was far from rare Indeed, the fact that he more or less accidentally came across six cases of typical Graves' disease—four in one family— in a brief journey through the country gave the impression that many more would be found on systematic inquiry Singer's description of the enlarged blood-vessels coursing and throbbing over the surface of an enormous trilobed growth pulling at the neck of an exhausted man of 27, seen at Goré in the west of the country, is especially vivid

Other earlier writers on goitre in *Ethiopia include Mérab,*[1018] who saw much of the disease at Tegoulet, Ankober and Djimema He mentions that a local method of treatment practised by the Gallas is to catch a live porcupine and apply it to the goitre in the manner of a leech; its sharp-pointed teeth puncture the gland in many places, drawing off great quantities of blood and a considerable amount of colloid fluid. In contrast to Singer's observations, Mérab regards exophthalmic goitre as exceedingly rare in Ethiopia

The most recent accounts of the Ethiopian plateau endemic are by Angelini & Scaffidi,[1015] by Gasperini [1016] and by Grassi Bertazzi [1017] Angelini & Scaffidi became acquainted with the disease during service in the Italo-Abyssinian campaign of 1936, when they were struck by the number of goitrous women who came for treatment to their field hospital at Enda Atzalà Chercòs.

Enda Chercòs, or Christ's House, lies in the Atzalà valley, one of many goitrous localities found throughout the region of Enda Meconni in southern Tigrai. The Enda Meconni endemic extends along the Alagi mountain range from the plains of Mai Mescic in the north to the depression of Mai Ceu in the south Beyond this area to the south, Angelini & Scaffidi

saw goitre in the Provinces of Wollo and Shoa where it was particularly evident at Debra Birhan and Ankober in the orbit of Addis Ababa They also refer to its prevalence in Wollega and Gojjam Provinces in the west of the country.

The high plateau of Scioa, on which the goitrous foci of Debra Sina, Debra Birhan, Ankober and Sciano are sited, has been closely studied by Grassi Bertazzi.[1017] He stresses the poor rye-flour diet, lack of vitamins, and adverse geochemical factors as contributory to goitre in this area.

Angelini & Scaffidi [1015] emphasize that it is almost solely the female sex that is affected; they saw scarcely any goitre among men and regard the predominance of cases in women as an indication of the mildness of the endemic, arguing that in regions where the disease is exceedingly severe the two sexes are affected almost to the same extent and, in addition, cretinism and deaf-mutism are always very pronounced They did not come across any cretins or deaf-mutes

On being asked their opinion as to the cause of the disease and the reasons for its widespread occurrence among women, some of the Atzalà valley people insisted on the particular importance of family mourning, which, in women, determines the cut of the hair; very often the commencement of a goitre is attributed to the shaving of the head at the time of the death of this or that relative. Others blamed the drinking-water, so often fouled by the decaying bodies of land animals and birds Mention was also made of a stream in the vicinity of Mai Mescic north of the Alagi range which bears the name Mai Gurgurì (i.e , goitre water) because those who habitually drink from it invariably contract goitre

Initial attempts by Angelini & Scaffidi to introduce iodine preventive measures were succeeded some years later by the more precise and systematic efforts of Gasperini [1016] He was especially concerned with goitre along the Eritrean border, where the chief endemic centres are a few small villages in the districts of Makale and Uagh, and in the neighbourhood of Adigrat Supplies of salt for this region are obtained in blocks from Massawa and other places on the Red Sea coastal area of Dancalia

Gasperini describes in detail the method by which this salt from the Eritrean salars was iodized and explains how he overcame certain difficulties connected with the process and with the subsequent distribution of the salt.

British Somaliland

Reporting in 1936 to the Economic Advisory Council's Committee on Nutrition in the Colonial Empire, the medical authorities in British Somaliland mentioned that they found some clinical evidence pointing to a possible deficiency of iodine in the diet of the Somalis, but it would appear that this cannot be very serious because the report specially stresses the distinctive stature and physique of the nomad Somalis and the absence of any widespread nutritional disorders [1021]

Uganda

Goitre does not appear to be a pressing problem in Uganda Nevertheless, nearly every Baganda child examined by Dean [1022] at a primary school in Kampala was found to have an enlarged thyroid. According to Dean no one has yet seen a Baganda cretin

In his paper on goitre in the Belgian Congo, van Campenhout [1023] refers to occurrences of the disease on the spurs of the Ruwenzori Mountains and in the basin of the Semliki river between Lake Albert and Lake Edward As the Ruwenzori range and the river Semliki form part of the western boundary of Uganda, this endemic area deserves mention here.

Tanganyika

There is little information about goitre in Tanganyika, but Trolli mentions its occurrence " in the mountainous regions " [1026] Since the context in which he was writing concerned the Belgian Congo and, in particular, the uplands around Lake Kivu and in the Ruanda-Urundi territory, it is possible that he was referring to the mountains of north-west Tanganyika immediately adjoining this area

More recently, C. D. Williams (personal communication, 1954) has recorded the presence of goitre specifically in the southern highlands

Belgian Congo and Ruanda-Urundi

Four distinct and well-documented regions of endemic goitre exist in the Belgian Congo These cover: (1) an upland area in the north and north-east, (2) the high mountain barrier separating the Belgian Congo from Uganda and Tanganyika in the east, (3) the mountainous parts of Katanga Province in the south and south-east; and (4) a smaller area in the far west situated just south-east of Léopoldville No goitre is reported from the vast low-lying parts of the Congo river basin in the centre of the country De Smet's [1032] impression is that a prevalence of between 1% and 2% occurs all over the country, rising to 80% in endemic areas of the north.

North and north-east

The first of these endemic regions extends throughout practically the whole of the area bounded by the Ubangi-Uele rivers in the north and the most northern stretch of the main Congo river It thus occupies a strip of territory about 600 miles in length, from Bangui and Zongo in the west to Niapu and Panga in the east, and about 150 miles in depth from north to south. Although the entire area is continuous so far as goitre occurrence is concerned, it may conveniently be considered in three main sections—west, centre, and east—by reason of the fact that the published literature on the subject naturally divides itself in this tripartite way

The western section, described more especially by Schotte,[1035, 1039] Daloze,[1026] van Campenhout,[1025] Baudart,[1023] and De Smet,[1032] covers the area watered by the rivers Ebola, Dua and Mongala. It includes the districts of Banzyville and Yakoma on the river Ubangi, and its most heavily affected focus is Abumombazi, which is situated at the headwaters of the Ebola.

The central section, referred to particularly by Rodhain,[1037] Trolli,[1026] van Campenhout,[1025] and De Smet,[1032] covers the area watered by the rivers Uele, Likati, Rubi and Itimbiri It includes the districts of Bondo on the river Uele, and Aketi and Buta on the river Rubi

The most easterly section of the endemic has been studied intensively by De Smet [1030, 1031] but has also been visited by Rodhain [1037] It covers the region watered by the rivers Lulu and Aruwimi, especially the triangle in the neighbourhood of Yangambi formed by the Aruwimi and the right bank of the upper Congo with apex at Basoko Eastward extensions of this goitrous area are found as far as Niapu near the source of the Rubi and at Panga on the river Ituri north-east of Stanleyville

According to natives of this northern Congo area goitre is of fairly recent origin there, and is said to date back only to about 1895 Van Campenhout,[1025] who spent much time in the Ebola-Likati area south and west of Bondo during the years 1894-97, was never particularly struck by the existence of the disease at that time, and Rodhain,[1037] who had lived in the Ubangi region since about 1900, only mentions his first cases in 1912-15 Following these early observations, reports of goitre occurrences mount up rapidly and the survey-map of the Ebola-Dua-Likati area made by van Campenhout in 1934 shows goitre rates of 20%, 30%, 50% and 60% Confirmatory data were given by Baudart [1023] in 1939, thus

	Number of people examined	*Number goitrous*	*Percentage goitrous*
North of the Ebola	4226	1649	39 02
South of the Ebola	4682	2442	52 16
Banks of the Uele	5661	345	6 09

In the Ebola region Baudart observed goitre quite frequently among infants at birth; but it is of course more prevalent in adults, especially women. To the east of this northern zone De Smet [1030] noticed an increasing prevalence (from about 1 5% to 80%) as he moved from Yangambi on the right bank of the upper Congo northwards towards the Aruwimi river On the left (south) bank of the Congo at this point the people are reported to be less afflicted by the disorder The explanation given is that centuries of rain have washed out all iodine from the soils on the northern bank whereas the alluvial soil of the south bank is being constantly reinforced with minerals from the river Among dwellers immediately on the river banks on either side, where much fish is consumed, there is no goitre Toxic goitre occurs in this area, and cases of goitrous fibroma in women are not uncommonly accompanied by sterility, a condition considered to be associated with hypersecretion of the sex hormone, folliculin (see also Velghe [1042])

East Congo and Ruanda-Urundi

Goitre centres have been found in various parts of the north-east and east of the Belgian Congo, particularly on the spurs of the Ruwenzori Mountains between Lakes Albert and Edward (van Campenhout [1025]), around Lake Kivu and in the Territory of Ruanda-Urundi at the head of Lake Tanganyika (Demaeyer & Vanderborght [1029]), and in the districts of Lokandu and Kasongo (Kadaner [1035] and Velghe [1012]) which lie on the river Lualaba, respectively 200 and 350 miles south of Stanleyville.

Ruanda, with a population of approximately two million, was made the subject of special study by Demaeyer & Vanderborght,[1029] who examined a total of 22 801 people of the Bahutu and Batutsi tribes—about a thousand from each of 22 different places The goitre rate varied from 1 83% to 28 37% according to locality, it was higher among women than among men and most goitres were of the parenchymatous type Nodular goitre was not observed in individuals under the age of 30, and no cretinism, deaf-mutism or Graves' disease was seen

The higher rates were usually found in places with a high rainfall and situated on lava and basaltic rocks rich in magnesium, calcium and potassium Dry regions on schists and quartzites had a low incidence The data for the 22 localities studied bring out this relationship (see Table XVI)

TABLE XVI PERCENTAGE PREVALENCE OF GOITRE IN RELATION TO RAINFALL AND NATURE OF ROCKS

Rainfall (mm)	Schists and quartzites	Granito-Gneiss and micaschists	Lavas and basalts
Below 800	4 66	—	—
800-900	2 04, 2 09, 2 92	1 83, 3 68	—
1000-1100	3.74	4 04	—
1100-1200	7 30, 14.73	17 62	—
1200-1300	11 19	17 57, 23.25	14 60, 25 24
1300-1400	6 25, 12 40	19 31	23 00
1500-1600	—	22 00	—
1700-1800	—	28 37	—

It will at once be seen that in a general way the percentages of goitre increase from top to bottom and from left to right of the table, that is, they increase with the degree of rainfall and, for the same level of rainfall, with the proportion of potassium, magnesium and calcium salts in the rocks

In Ruanda, " vegetable " salt used to be eaten but has been completely replaced by ordinary salt and cannot therefore be associated with the

presence of goitre. Among the different vegetables eaten by the Bahutu and Batutsi only one has any relationship with the *Brassica* genus, this is "isogo" (*Erucastrum arabicum*), but as it is in almost general use both in areas of high and in those of low incidence, it does not seem that it can be incriminated as goitrogenic

The goitres mentioned by Kadaner [1035] at Lokandu in the Maniema region occur predominantly in women and are not regarded as very serious; those seen by Velghe [1012] among the Matapa at Kasongo were also mostly in women, but apparently in this district sterility and goitre go hand in hand. Lack of iodine in the soil and water is not considered to be primarily responsible for the frequency of goitre here, since the disease is much less prevalent in neighbouring communities living in an identical environment. It is believed that the sterility among women is due to a conditioned deficiency of iodine produced by an excessive secretion of the sex hormone, folliculin, acting as a goitrogenic agent Men are less affected with thyroid trouble because their testosterone secretion is generally normal in amount (see also De Smet [1030])

South and south-east

The southern endemic covers the greater part of the highlands of Katanga Province. With its centre at Sampwe in the Kundelungu Mountains, where prevalence is highest, it extends to Mwanza in the north, almost to Elisabethville in the south, as far east as Pweto on Lake Mweru, and westward through Bukama, Kalule, Kamina and the Lomami country to the river Lulua and the Dilolo area on the borders of Angola (Schotte, [1038, 1039] Trolli;[1026] van Campenhout;[1025] Calonne [1024])

The Sampwe district, examined closely by Calonne,[1024] is situated in the valley of the river Lufira, a tributary of the Lualaba. It is surrounded by mountain masses yielding a multitude of small streams near to which are established native settlements consisting chiefly of the Basela and Balomotwa tribes These people live a hard and frugal life, as a general rule sowing only one crop on an impoverished soil, possessing few if any livestock, and all obtaining their drinking-water from the same mountain sources

The disease is seen only at lower levels along the margins of the rivers feeding the Lufira, not on the high plateaux The over-all rate of established goitre among 1118 natives examined by Calonne was 24 5% If 71 cases of diffuse hypertrophy seen in young people about the age of puberty are included in addition, the over-all rate increases to 30 8%. Men were less affected than women, out of 395 males of all ages there were 34 with goitre (8 6%) compared with 240 cases among 723 females examined (33 2%) Certain districts were intensely affected, with rates among women of 50%, nevertheless, as is not unusual in goitre country, some villages situated in the very heart of the affected area were, inexplicably, entirely free from the disease

East Congo and Ruanda-Urundi

Goitre centres have been found in various parts of the north-east and east of the Belgian Congo, particularly on the spurs of the Ruwenzori Mountains between Lakes Albert and Edward (van Campenhout [1025]), around Lake Kivu and in the Territory of Ruanda-Urundi at the head of Lake Tanganyika (Demaeyer & Vanderborght [1029]), and in the districts of Lokandu and Kasongo (Kadaner [1031] and Velghe [1012]) which lie on the river Lualaba, respectively 200 and 350 miles south of Stanleyville.

Ruanda, with a population of approximately two million, was made the subject of special study by Demaeyer & Vanderborght,[1029] who examined a total of 22 801 people of the Bahutu and Batutsi tribes—about a thousand from each of 22 different places The goitre rate varied from 1.83% to 28 37% according to locality, it was higher among women than among men and most goitres were of the parenchymatous type Nodular goitre was not observed in individuals under the age of 30, and no cretinism, deaf-mutism or Graves' disease was seen.

The higher rates were usually found in places with a high rainfall and situated on lava and basaltic rocks rich in magnesium, calcium and potassium Dry regions on schists and quartzites had a low incidence The data for the 22 localities studied bring out this relationship (see Table XVI)

TABLE XVI PERCENTAGE PREVALENCE OF GOITRE IN RELATION TO RAINFALL AND NATURE OF ROCKS

Rainfall (mm)	Schists and quartzites	Granito-Gneiss and micaschists	Lavas and basalts
Below 800	4.66	—	—
800-900	2.04, 2.09, 2.92	1.83, 3.68	—
1000-1100	3.74	4.04	—
1100-1200	7.30, 14.73	17.62	—
1200-1300	11.19	17.57, 23.25	14.60, 25.24
1300-1400	6.25, 12.40	19.31	23.00
1500-1600	—	22.00	—
1700-1800	—	28.37	—

It will at once be seen that in a general way the percentages of goitre increase from top to bottom and from left to right of the table, that is, they increase with the degree of rainfall and, for the same level of rainfall, with the proportion of potassium, magnesium and calcium salts in the rocks.

In Ruanda, " vegetable " salt used to be eaten but has been completely replaced by ordinary salt and cannot therefore be associated with the

valley area The majority of the Lala dwell in the highlands; the rest live in the lowland valleys through which run the Lukusashi, Luangwa and Lunsemfwa rivers, which receive the streams and tributaries arising on the Zambesi side of the Congo-Zambesi watershed

Beet[1044] made an exhaustive nutritional survey of 660 Lala children at 17 schools in both plateau and valley areas He found 38% of children with enlarged thyroids The rate was higher in girls but the difference was not marked. To the north-east of Serenje and Mkushi, but in the same general area, lies Chitambo, where D Mackay (personal communication, 1946) has reported the prevalence of goitre

There is very little published information about goitre in Southern Rhodesia but, according to W. R. Carr (personal communication, 1954), the disease is endemic in many parts This is confirmed by the decision of the Government (1954) to consider the iodization of all crude salt, of which about 10 000 tons are consumed annually in Southern Rhodesia As this supply comes from a number of different local sources, the iodization of all consignments presents an administrative problem Enrichment of crude salt with potassium iodate is carried out in Salisbury, but its distribution can be extended only by improved health education Refined salt is now more popular in the Rhodesian market, and on this account proposals have been made to import, or to produce locally, packeted iodized table salt [1045]

Iodine deficiency among domestic animals in Southern Rhodesia has been pin-pointed by Affleck [1043] in the Karoi area, on farms along the south bank of the river Hunyani near Sinoia, and at Raffingora where also the native population is goitrous In this same area to the north of Salisbury, Affleck has seen enlarged thyroids and skeletal deformities among foals in the Umvukwe Range Here, interference with iodine utilization due to the high cyanogen content of wilted lucerne is believed to be a contributory factor. After a particularly wet season in 1958, a sudden increase in the number of cases of stillbirth and weakness at birth among goat kids was reported at Victory Block between Raffingora and the Umvukwes, the animals were born with very large thyroids and were frequently hairless

Union of South Africa and neighbouring territories

Following the general north-south pattern of this world survey, it is convenient to treat the southern section of the African continent as a whole. Accordingly, the Union of South Africa is considered together with its neighbouring territories, more or less in the following order: the Caprivi Strip, South-West Africa, Bechuanaland, Swaziland, and Basutoland. The main centres, features, and causes of endemic goitre in this vast area are fully documented and described by Steyn and his colleagues in the 1955 report of the South African Goitre Research Committee [1065] Among others

Toxic goitres develop in about 25% of cases, and an interesting observation is that clinical signs of hyperthyroidism, especially in girls, are quickly brought on by any unusual physical exertion—running a race, for example. Congenital goitrous defects—idiocy, deaf-mutism and cretinism—are very frequent in the Sampwe area

Western Belgian Congo

Medical census of the population of the Province of Kasai towards the west-centre of the Belgian Congo, and of the Lower Congo District in the extreme west, reveals only isolated occurrences of goitre (Trolli [1026]). There is, however, a mildly endemic centre in the Foréami *cercle* of Popokabaka, an area occupied by the Bayaka tribe about 150 miles south-east of Léopoldville It covers the region watered by the rivers Kwango, Twana and Wamba, and it extends to the Mosamba country east of the Wamba. Himpe & Pierquin,[1033] Vande Voorde,[1010] and Delaunoy & Claeys [1028] are the authorities on this endemic

The staple diet of the natives is " monwa " (cassava) and is the same for all regions of the *cercle* The yam is in fairly widespread use, and to a lesser extent rice and maize By way of condiments there are gourds, peanuts, grasshoppers, caterpillars, a few cooked vegetables and pimento The survey by Himpe & Pierquin [1033] relates to a total of 36 316 persons in the administrative sectors of Ngowa, Munene and Kabula among whom they found only 303 goitres The prevalence is therefore slight, being on an average 0 83% and nowhere higher than 4 25% Goitre runs very distinctly in families, starting at an early age and developing slowly to maturity in adult life In regard to size, the 303 enlargements varied considerably and are classified thus.

Pigeon's egg	78	Fist size	71
Hen's egg	90	Baby's head	16
Duck's egg	45	Football	3

There are few complications, goitre does not apparently influence fertility, and hyperthyroidism if it occurs at all is not acute.

Finally, so far as the goitre geography of the Belgian Congo is concerned, Perin [1036] has noted that the disease is frequent in the Kimvula area of the Lower Congo to the west of Popokabaka Here, the people are of poor physique, anaemia is common, and there is marked lumbar curvature and a high proportion of pelvic malformations in women, leading to difficulties at childbirth

The Rhodesias

The Districts of Serenje and Mkushi in the Central Province of Northern Rhodesia are areas of endemic goitre The region, occupied for the most part by the Lala, a Bantu tribe, consists of a wooded highland plateau and a

Barakwengo, the goitre rate was almost 70%; among the Okavango, 62 6%.

Of all the enlarged thyroids examined by Kuschke only a few were nodular and one definitely in an early carcinomatous stage. He attributes the disease to iodine deficiency in the food, water and soil of the area and recommends that iodized salt be supplied not only throughout the whole of the Caprivi Strip but also to the tribes of the neighbouring Okavango Native Territory.

For the rest of South-West Africa there are no definite facts, but Steyn et al.[1065] suggest that as the subterranean waters in the southern semi-arid regions of the country contain fluorine, there is every likelihood that fluorine-induced goitre occurs there just as it does in the adjoining areas of north-western Cape Province, also known to be fluorine-rich.

Bechuanaland Protectorate

Goitre is seen in Bechuanaland only in the far north, where the country marches the whole length of the Caprivi Strip As already mentioned, there is a high prevalence in this area, especially along the Linyanti river to the east and along the Okavango river in the extreme north-west of the Protectorate. Elsewhere in the country only occasional cases of goitre are met with (B T. Squires—personal communication, 1955)

Union of South Africa, Swaziland and Basutoland

Taking the Union, Swaziland and Basutoland as a whole, goitre is found in the following five main areas:

1. *Transvaal* A narrow belt stretching for 300 miles across Transvaal from Zeerust in the west through Witwatersrand as far as Nelspruit in the east. Places affected in this endemic area (from west to east) are Zeerust, Groot Marico, Kuilfontein, Koster, Rustenburg, Brits, Bronkhorstspruits (just east of Pretoria), Belfast, Machadodorp, Waterval Boven, Elandshoek Valley, Nelspruit and Barberton.

2 *Swaziland* From the Nelspruit and Barberton area of eastern Transvaal the goitre belt curves southward and occupies practically the whole of Swaziland

3. *Basutoland and the Drakensberg range* The entire Drakensberg area, including Basutoland, is potentially goitrous On the northern slopes of the range the disease occurs at Witzieshoek in the Orange Free State. On the eastern side it is found along Bushman's river and also in the Estcourt and Helpmakaar areas of Natal. Somewhat farther south on the eastern Drakensberg there are occurrences at Impendhle, Polela and Underberg Goitre has also been noted in and around Blikana and Herschel which lie at the foot of the Witteberg range in Cape Province just beyond the southern border of Basutoland Qumbu on the south-eastern edge of

who have made notable contributions to knowledge of goitre in South Africa are Frack[1051] (Transvaal); Blom,[1048] Buttner[1047] and Schur Brown[1061] (Langkloof Valley); Dormer[1049] (Natal), Le Riche[1054] (Johannesburg); Kark & Le Riche[1052] (Orange Free State and Natal), and Steyn's collaborators, Malherbe & Osburn[1053 1057]

Eastern Caprivi Strip

As mentioned on page 131, goitre is prevalent in the narrow strip of territory running between the south of Angola and the north of Bechuanaland to connect South-West Africa with the Rhodesias The Caprivi Strip is some 200 miles long and 20-30 miles wide, with a total area of approximately 4500 square miles (about 11 500 km²) and a population of about 15 000 The country is flat and very sandy, except in the most low-lying areas which grow luxuriant crops During the rainy season large tracts are inundated The nutritional state of the people appears satisfactory but their standard of hygiene is low, and, owing to the marshy nature of much of the country, malaria is rife

In 1942, Annecke (see Steyn et al[1063]) made a goitre survey of the Eastern Caprivi Strip and reported that " anything above 70 per cent of men, women and children show a simple enlargement which in older age may become nodular (probably adenomatous) " He found the disease predominantly in females and suggested a relationship between its occurrence and the distribution of the manketti- or mungongo-nut tree. It was subsequently proved, however, that the manketti nut has no goitrogenic properties B. T Squires (personal communication, 1955) visited the south-eastern portion of the Eastern Caprivi Strip in 1949 and reported a 50% goitre rate there, enlarged thyroid glands in breast-fed babies were no exception In this area manketti-nut trees are extremely rare

The more recent observations by the South African Goitre Research Committee (Steyn et al[1063]) confirm the high prevalence in the Eastern Caprivi Strip, even among breast-fed infants and toddlers. The mean goitre rate throughout the area is 50%, but at Linyanti village it rises to 70% From the results of their investigations the Committee conclude that the major cause of the endemic is a primary iodine deficiency in soil, water and food, aggravated no doubt by the contamination of drinking-water and general unhygienic conditions

Western Caprivi Strip and South-West Africa

A goitre survey of the western portion of the Caprivi Strip, which for administrative purposes falls under the jurisdiction of South-West Africa, has been made on behalf of the South African Goitre Research Committee by Kuschke.[1065] He found that the endemic of the eastern strip extends westward and affects the tribes inhabiting the western end of the strip and the adjoining areas of South-West Africa and Bechuanaland. Among the

Barakwengo, the goitre rate was almost 70%; among the Okavango, 62.6%.

Of all the enlarged thyroids examined by Kuschke only a few were nodular and one definitely in an early carcinomatous stage. He attributes the disease to iodine deficiency in the food, water and soil of the area and recommends that iodized salt be supplied not only throughout the whole of the Caprivi Strip but also to the tribes of the neighbouring Okavango Native Territory.

For the rest of South-West Africa there are no definite facts, but Steyn et al.[1065] suggest that as the subterranean waters in the southern semi-arid regions of the country contain fluorine, there is every likelihood that fluorine-induced goitre occurs there just as it does in the adjoining areas of north-western Cape Province, also known to be fluorine-rich.

Bechuanaland Protectorate

Goitre is seen in Bechuanaland only in the far north, where the country marches the whole length of the Caprivi Strip. As already mentioned, there is a high prevalence in this area, especially along the Linyanti river to the east and along the Okavango river in the extreme north-west of the Protectorate. Elsewhere in the country only occasional cases of goitre are met with (B T. Squires—personal communication, 1955)

Union of South Africa, Swaziland and Basutoland

Taking the Union, Swaziland and Basutoland as a whole, goitre is found in the following five main areas:

1. *Transvaal* A narrow belt stretching for 300 miles across Transvaal from Zeerust in the west through Witwatersrand as far as Nelspruit in the east Places affected in this endemic area (from west to east) are Zeerust, Groot Marico, Kuilfontein, Koster, Rustenburg, Brits, Bronkhorstspruits (just east of Pretoria), Belfast, Machadodorp, Waterval Boven, Elandshoek Valley, Nelspruit and Barberton.

2. *Swaziland.* From the Nelspruit and Barberton area of eastern Transvaal the goitre belt curves southward and occupies practically the whole of Swaziland.

3 *Basutoland and the Drakensberg range* The entire Drakensberg area, including Basutoland, is potentially goitrous On the northern slopes of the range the disease occurs at Witzieshoek in the Orange Free State. On the eastern side it is found along Bushman's river and also in the Estcourt and Helpmakaar areas of Natal Somewhat farther south on the eastern Drakensberg there are occurrences at Impendhle, Polela and Underberg Goitre has also been noted in and around Blikana and Herschel which lie at the foot of the Witteberg range in Cape Province just beyond the southern border of Basutoland. Qumbu on the south-eastern edge of

who have made notable contributions to knowledge of goitre in South Africa are: Frack[1051] (Transvaal), Blom,[1046] Buttner[1047] and Schur Brown[1061] (Langkloof Valley), Dormer[1049] (Natal); Le Riche[1054] (Johannesburg); Kark & Le Riche[1052] (Orange Free State and Natal); and Steyn's collaborators, Malherbe & Osburn[1053, 1077]

Eastern Caprivi Strip

As mentioned on page 131, goitre is prevalent in the narrow strip of territory running between the south of Angola and the north of Bechuanaland to connect South-West Africa with the Rhodesias. The Caprivi Strip is some 200 miles long and 20-30 miles wide, with a total area of approximately 4500 square miles (about 11 500 km²) and a population of about 15 000 The country is flat and very sandy, except in the most low-lying areas which grow luxuriant crops During the rainy season large tracts are inundated The nutritional state of the people appears satisfactory but their standard of hygiene is low, and, owing to the marshy nature of much of the country, malaria is rife.

In 1942, Annecke (see Steyn et al[1065]) made a goitre survey of the Eastern Caprivi Strip and reported that "anything above 70 per cent of men, women and children show a simple enlargement which in older age may become nodular (probably adenomatous)". He found the disease predominantly in females and suggested a relationship between its occurrence and the distribution of the manketti- or mungongo-nut tree. It was subsequently proved, however, that the manketti nut has no goitrogenic properties. B T. Squires (personal communication, 1955) visited the south-eastern portion of the Eastern Caprivi Strip in 1949 and reported a 50% goitre rate there; enlarged thyroid glands in breast-fed babies were no exception In this area manketti-nut trees are extremely rare

The more recent observations by the South African Goitre Research Committee (Steyn et al[1065]) confirm the high prevalence in the Eastern Caprivi Strip, even among breast-fed infants and toddlers. The mean goitre rate throughout the area is 50%, but at Linyanti village it rises to 70% From the results of their investigations the Committee conclude that the major cause of the endemic is a primary iodine deficiency in soil, water and food, aggravated no doubt by the contamination of drinking-water and general unhygienic conditions

Western Caprivi Strip and South-West Africa

A goitre survey of the western portion of the Caprivi Strip, which for administrative purposes falls under the jurisdiction of South-West Africa, has been made on behalf of the South African Goitre Research Committee by Kuschke.[1065] He found that the endemic of the eastern strip extends westward and affects the tribes inhabiting the western end of the strip and the adjoining areas of South-West Africa and Bechuanaland. Among the

The prevalence of goitre throughout the Union and neighbouring territories of South Africa varies considerably. Malherbe found that 26 6% of children at Kuilfontein School (Oberholzerskloof) in the south-western Transvaal were affected, but at one place in the Nelspruit-Barberton area on the east side of the Transvaal no less than 290 Bantu women out of 300 examined had goitre. In Swaziland the rates among school-children are generally high, varying from 4% at Goedgegun European School to 71% at Imbuluzi Native Mission School 11 miles north of Mbabane.

Among Natal schoolchildren the incidence is apparently considerably lower than in the Transvaal. Strydom (see Steyn et al [1065]) carried out a thyroid survey at 14 European, 9 Coloured and 6 Native Schools in Natal and found rates ranging from zero in the European Schools to 4% in the Native Schools

Thirty-three years ago (1927) about 65% of the inhabitants in the Krakeel, Hoeree and Klein river valleys (Langkloof-Kouga region) showed simple thyroid enlargement More recent statistics from this area are 23% of slightly enlarged glands in Coloured children at a school in Knysna, and rates varying from 3% in primary and secondary schools at Joubertina to 22% at Opkoms School Rates of 7% to 25% are recorded by the South African Goitre Research Committee among children in the endemic fluorosis areas of north-western Cape Province.

During the course of their investigations the Goitre Research Committee encountered many cases of simple goitre which were intermittently toxic By far the highest prevalence of thyrotoxicosis, including exophthalmic goitre, was seen in north-western Cape Province. Steyn and his colleagues believe that the fairly general use of large amounts of iodine in the form of Lugol's solution for the treatment of simple goitre is in some measure responsible for the high prevalence of thyrotoxicosis here. This raises once more the evergreen problem of Jod-Basedow or iodine-induced hyper-thyroidism.

On the question of causation, all the information collected in the course of the exhaustive analytical investigations conducted by the South African Goitre Research Committee has amply confirmed the view that iodine deficiency is the primary cause of endemic goitre in the Union and neighbouring countries Contributory factors in certain areas already mentioned are excessive quantities of fluorine in the drinking-water Soils, waters and vegetation extremely rich in available calcium are also incriminated in some localities as, for instance, the Langkloof Valley region It has also been suggested by Buttner [1017] that the occurrence of the element tellurium in the Knysna area may be a contributory etiological factor, but there is no confirmation of this.

The Goitre Research Committee, headed by Steyn, strongly recommend the non-compulsory introduction of iodized salt in all the endemic goitre

the Drakensberg is another goitre centre falling within this geographical group

Exact information on the degree of prevalence of goitre in Basutoland was practically non-existent until the report of a survey conducted in 1957-58 by Muñoz & Anderson [1059] recently became available. Seven of the nine districts of the country were covered by the survey which involved the examination of 13 284 individuals of both sexes, of all ages, and from lowlands, foothills and mountains An average prevalence of endemic goitre (mainly diffuse) of 41 %, with a range of from 30 % to 50 % according to district, was exposed The problem is thus a serious one, and the authors recommend the use of salt iodized at a level of 1 part of potassium iodate in 10 000-20 000 parts of salt

4 *Southern Cape Province* In the south-east of Cape Province goitre occurs in the Winterberg area and in places along the river Kei, which rises in these mountains. Fort Beaufort, to the south of the Winterberg, is a goitre centre

In the extreme south of the Province the whole of the region from Prince Albert and the Groot Zwartberg eastward to Humansdorp and Port Elizabeth is a well-known goitre area It includes (from west to east) Schoemanshoek; the Outeniquas Mountains and the neighbourhood of George and Knysna; Uniondale, Krakeelrivier, the Hoeree valley, Kleinrivier, Joubertina, and other places in the Kouga Mountains and Langkloof-Kouga river valleys

In the south-west of Cape Province goitre has been noted at Villiersdorp, Greyton and Caledon to the south-east of Cape Town; and also at Ceres and Prince Alfred's Hamlet in the Hexrivierberg region to the north-east of Cape Town.

5. *North-western Cape Province.* Goitre occurs throughout the entire area from the coast at Port Nolloth eastwards for 300 miles to Kenhardt This belt includes Springbok, Nababeep and Ookiep; Poffadder; and Kakamas and Upington on the Orange river Another 200-300 miles to the north and east of Kenhardt, the disease is found at such places as Kuruman and Vryburg

Chemical analysis of water in these regions led Steyn et al [1065] to conclude that endemic goitre in the north-western Cape Province is chiefly due to the general presence of goitrogenic quantities of fluorine and calcium in the drinking-water and not to an inherent primary iodine deficiency. There are, *of course, exceptions Areas exist in the north and north-western parts* of Cape Province where goitre is due, in a measure at least, to an absolute iodine deficiency; this is the case, for example, at Upington and Kuruman And there is the fact, as yet unexplained, that the prevalence among scholars at Port Nolloth and Vryburg is fairly high in spite of a very satisfactory concentration of iodine and a minimal amount of fluorine in the municipal water-supplies

The prevalence of goitre throughout the Union and [illegible] territories of South Africa varies considerably. Malherbe [illegible] 26.6% of children at Kuilfontein School (Oberholzers[illegible]) [illegible] western Transvaal were affected, but at one place in the [illegible] berton area on the east side of the Transvaal no less than [illegible] out of 300 examined had goitre In Swaziland the [illegible] children are generally high, varying from 4% at G[illegible] School to 71% at Imbuluzi Native Mission School [illegible] Mbabane

Among Natal schoolchildren the incidence is [illegible] lower than in the Transvaal Strydom (see Steyn et al. [illegible] thyroid survey at 14 European, 9 Coloured and 6 Native [illegible] and found rates ranging from zero in the European [illegible] the Native Schools.

Thirty-three years ago (1927) about 65% of the [illegible] Krakeel, Hoeree and Klein river valleys (Langkloof-[illegible]) simple thyroid enlargement. More recent statistics [illegible] of slightly enlarged glands in Coloured children [illegible] rates varying from 3% in primary and secondary [illegible] 22% at Opkoms School Rates of 7% to 25% [illegible] African Goitre Research Committee among children [illegible] areas of north-western Cape Province.

During the course of their investigations the [illegible] encountered many cases of simple goitre [illegible] By far the highest prevalence of thyrotoxic [illegible] goitre, was seen in north-western Cape Province [illegible] believe that the fairly general use of large [illegible] Lugol's solution for the treatment of [illegible] responsible for the high prevalence of [illegible] once more the evergreen problem of [illegible]

areas where the disease is due to a primary iodine deficiency, i e., in every goitre area throughout the Union except in those parts of the north-western Cape Province where goitre is fluorine-induced [1065]

Thyroid disease is surprisingly uncommon among farm animals in the endemic goitre areas of South Africa, but occasional cases are seen. When investigating stock diseases all over the Union and in South-West Africa, the Eastern Caprivi Strip and Swaziland, Steyn & Sunkel [1063] only twice saw evidence of iodine deficiency in animals The first was in a small area in the Orange Free State where merino ewes gave birth to a high percentage of lambs with enlarged thyroids and a number of stillborn lambs. The second occasion was an outbreak of goitre among newborn Afrikander calves on a farm situated on the south bank of the Black Kei river in the Cathcart district of Cape Province. The only other recorded occurrence of goitre in Afrikander calves is that cited by Matthew & Thomas [1058] on a farm in the eastern Cape Province. According to a recent report (1956) there is no iodine deficiency among animals in the Highveld region around Potchefstroom west and south-west of Johannesburg [1050]

Seychelles and Madagascar

Minor occurrences of goitre have been noted in urban and rural areas of the Seychelles by M. Dick (personal communication, 1952), and in the mountainous interior of Madagascar by Cloitre [1069] and by Nimier (see Dupont [1000])

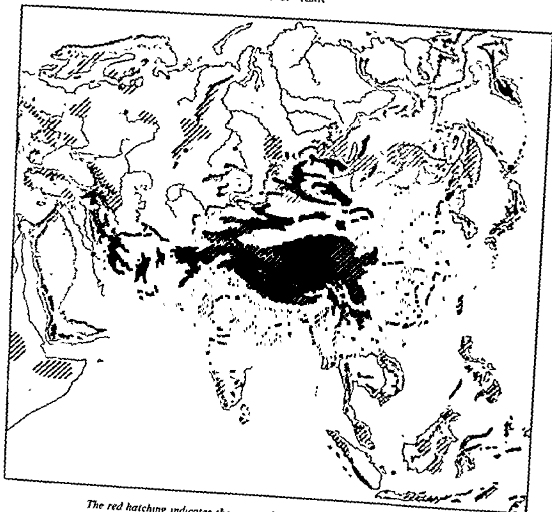
Cases seen in Madagascar are mostly of sporadic and unrelated occurrence among Betsiléo and Hovas women who come from such districts on the high plateaux as Ambositra, Ambohimahasoa, Fianarantsoa and Alakamisy-Itenina The disease is unknown among the Tanalas, Baras and other peoples of the eastern coast region and extreme south of the island

Nimier (see Dupont [1000]) found no more than 50 goitres in 60 000 inhabitants of the Ambositra district, and Cloitre [1069] emphasizes that there are no grounds for regarding the disease as seriously endemic in Madagascar. Of 32 cases seen by him, 31 were in women over 25 and mostly between 35 and 50 years of age. Visible thyroid swelling in adolescent girls was not uncommon.

Asia

The headquarters of goitre and cretinism on the continent of Asia are the northern and southern slopes of the Himalaya Mountains This classic endemic focus extends eastwards almost without interruption through Burma into China and neighbouring countries The adjacent endemic areas of southern Asiatic Russia have already been noted (see pp. 75-76) In the western regions of Asia goitre occurs endemically only here and there; a few places in Turkey are mildly goitrous, and there are centres in Lebanon and in Iran.

FIG. 6. ASIA



The red hatching indicates the areas where endemic goitre has been found

With the exception of Lebanon, the countries along the Levantine coast—Syria, Israel and Jordan—are apparently goitre-free, as also are Iraq and Arabia, although it is said that goitre has been seen on the Yemen-Aden border.

Turkey

Speaking generally, goitre is not a serious problem in Turkey. Nevertheless, the fact emerged during discussions at the Tenth National Medical Congress, held at Ankara in 1948, that one or two areas may be regarded as endemic.[1071] One of these covers the northern bulge of Turkey where steep valleys from the spurs of the Kastamonu-Ilkaz mountains slope sharply to the southern shores of the Black Sea. Goitre maps of this general area of northern Anatolia have been made by Eser [1071] and by S N. Yorukoglu (personal communication, 1958). These show black spots at Adapazarı, Düzce and Bolu, the environs of Bartın, Zonguldak, Kastamonu, Taşköpru, and Gerze; and on the peninsula at Sinop Somewhat farther east, goitre has been found in the district of Amasya, and at Rize, a town on the extreme south-east coast of the Black Sea

Another endemic region lies to the west and south-west of the country; here the principal centres are Afyon, Aydın and the neighbourhood of the Menderes Chai river south-east of Smyrna, and Isparta, which is recognized as an area of pronounced goitre The Isparta focus has been studied especially by Eser & Velicangil [1072, 1073] who found rates of 35% among boys of 12 to 16 years of age, and of 56% among women between 16 and 60, with the maximum frequency at 16 to 19 years In the southern bulge of the Turkish mainland opposite Cyprus, goitre is found in the Bozkir and Ermenek Districts of Konya Province and in the Taurus Mountains. In the eastern part of Turkey there are centres of the disease at Erzincan and Erzurum relatively near the endemic areas of Armenia and the Caucasus

According to Saka,[1075] the city of Istanbul and the country surrounding the Sea of Marmara, as well as the regions westward into Thrace, are practically goitre-free, although cases of thyrotoxic disease appear to be frequent. Saka examined the thyroids of 71 persons from all parts of Turkey who had died from a wide variety of diseases. He found the average weight of the normal gland to be 26 6-28 0 g. Weights above average were noted in persons who came exclusively from districts of high elevation where goitre is of frequent occurrence, e g, from Bartın (42 5 g and 80 g), Djerkesch (44 g), Erzincan (49 g) and Erzurum (43 g and 55 g)

Animal goitre is not uncommon in Turkey, particularly in the northern Kastamonu-Ilkaz region Akçay [1070] examined the thyroid glands of 177 cattle post mortem; of these, 125 were affected with simple hyperplastic goitre, 9 had colloid goitres and 8 were exophthalmic

Since about 1945 the inhabitants of goitre regions in Turkey have been supplied with iodized salt, and goitre posters and pamphlets have been distributed [1074]

Lebanon

Physiographically the Lebanon consists of two parallel mountain chains running the length of the country in a NE-SW direction—the Lebanon range proper to the west, and the Anti-Lebanon to the east. Between these two ridges is a high plateau, the Bekaa

Goitre is endemic at several places on the slopes and in the valleys of these mountains, particularly those on the inner sides facing the Bekaa plain in the central section of the country. Ciaudo et al [1080] give the following origin of 100 cases they had occasion to observe.

Kab-Elias	18
Zahlé	15
Deir El Harf	14
Hamana	13
Beskinta	6
Hasroun	4
Broumana	3
Salima	3
Miscellaneous	24
Total	100

Kab-Elias is situated on the eastern slope of the main Lebanon chain, and overlooks the Bekaa Zahlé is similarly placed, deeply recessed between two mountains It is impossible to walk along the streets of these two villages without noticing goitrous people

In the narrow coastal strip between the Mediterranean Sea and the western Lebanon foothills the disease is practically non-existent. Among the 24 miscellaneous cases listed above, only four came from the seaboard· one from Gebeil (Byblos), one from Chekka, one from Jounieh and the fourth from Chiah All these subjects, although born by the sea, were descended from goitrous parents of mountain stock It is exceptional if not impossible to find a Beirut native with goitre; any cases that may be seen there have originated elsewhere

The goitres seen in the Lebanese mountains are of the diffuse parenchymatous type and often of considerable size; toxic symptoms are not uncommon, and malignancy is occasionally met with. Chaia [1077] has made the interesting observation—reminiscent of that by Calonne [1024] in the Belgian Congo (see page 142)—that excessive or unusual physical effort may induce thyroid enlargement. He noticed that goitre developed in a number of young soldiers under hard training within six months of enlistment.

The social implications of goitre in the mountain areas of Lebanon, and the need to institute preventive measures, have been emphasized by

Refet[1081] He proposes the following regime for eventually ridding the country of goitre:

(1) Examination by the district doctor of all primary schoolchildren between the ages of 7 and 14 years, to eliminate if possible those who might be sensitive to iodine medication

(2) First year of prophylaxis: give each child one tablet of Iodostarin (diiodotariric acid) or one tablet containing 0.001 g of sodium or potassium iodide, regularly every Monday morning for 40 weeks Stop during the holidays.

(3) Second year of prophylaxis: one Iodostarin or iodide tablet per child once a week for four weeks during each half-year.

(4) Third and fourth years of prophylaxis: continue the tablets weekly for one month every half-year, as in the second year of prophylaxis, in cases where the goitre has not disappeared.

An appraisal of radioiodine tests in the diagnosis of thyroid function in Lebanese people has been made by Abu Haydar.[1076]

Israel

Recent mass immigrations into Israel of Jews from all over the world—people with different cultural, nutritional and climatic backgrounds which they have tended to preserve in the new environment—provided Feldman[1082] with an opportunity to examine whether these differences are reflected in the prevalence and type of thyroid disease in Israel. His study relates to Jewish people in three groups of origin: *European-American*, *African-Asian*, and native-born Israelis.

Thyroid glands taken at consecutive autopsies from 72 unselected Jewish children under 15 years of age were of normal weight and showed no pathological lesions. Of a total of 323 patients treated either surgically or medically for thyroid disease during life in the five years from 1948 to 1953, only five were infants or children under 15 years.

From these facts Feldman concludes that Israel is not a country where goitre is endemic.

As for the adult population, Feldman found that 42 thyroids out of 110 taken at consecutive autopsies from individuals over 15 years old showed pathological change—a rate of 38% in random adult *post mortem* examinations. The rate of thyroid disease among all adults clinically examined by him during life for any reason whatsoever was 7 per 1000, or approximately fifty times less than that disclosed after death. The reason [illegible] and clinical findings: the

The type of pathological change seen after death was more or less the same for all adults irrespective of birthplace. In the clinical material,

thyroid disease was observed more frequently in patients of European-American origin. Feldman concludes from this that Jews born in Europe and America either acquire more severe thyroid disease than the other two groups or are more prone to seek medical aid.

Those interested in goitre occurrence among Jewish peoples in Europe will find Greenwald's views absorbing.[787]

Iran

Two centres of goitre occurrence have been noted in Iran. These are the villages of Alischavaze and Kereshtek about 25 miles from Teheran. The possibility of introducing iodized salt in this locality is being explored by M. B. Mashayekhi (personal communication, 1953). Gaguik of the medical school at Teheran University is testing the iodine content of different waters in Iran in relation to goitre occurrences there.

The Indian peninsula [a]

The severe manifestations of goitre in the south-eastern Soviet Republics of Uzbek, Tadzhik and Kirgiz, on the Pamir plateau, and in other remote centres on the northern slopes of the central Asiatic massif (see page 75) are repeated with equal intensity on the Indian side of this great mountain barrier. In fact, the northern frontiers of the Indian peninsula extending from Afghanistan through Kashmir and Jammu eastwards for more than 1500 miles along the southern valleys and foothills of the Himalayas into Assam and Burma have a goitre reputation more formidable perhaps than that of any other part of the world The intensity of the disease is so great in some places as to merit the term hyper- or super-endemic (Stott & Gupta [1128]) The goitre literature of the various countries that make up the Indian peninsula is intermingled to such a degree that it is dealt with here as a whole, and not necessarily with reference to political boundaries.

Geographical distribution

Descending into the north of West Pakistan from the mountain passes of Afghanistan and Badakhshan—areas themselves not immune [372]—one enters the western end of the goitre zone at Chitral, a wild and desolate region mountain-girt and mountain-intersected by the precipitous spurs and slopes of the Hindu Kush. Immediately to the east, in the north of Kashmir at the head-waters of the Indus, lies the district of Gilgit which, together with Chitral, is famed in the annals of goitre and cretinism by the researches of McCarrison [1101, 1102, 1125] In the North-West Frontier Province of Pakistan, on the edge of Kashmir, a considerable amount of goitre has been observed by H W. Waite (personal communication, 1954) in the Kagan valley and hills of Hazara, and by French et al.[1092] and Watkin et al [1130] at Muzaf-

[a] Includes Afghanistan, Pakistan, Kashmir, Nepal, Tibet, India and Assam

farabad From Gilgit the goitre belt extends south-eastwards through Kashmir along the Karakoram range and over the districts of Baltistan and Ladakh into the north-west of India proper.[1083, 1119]

Here, the endemic pervades the sub-Himalayan regions of Himachal Pradesh (Kangra, Pathankot, Gurdaspur, Hoshiarpur, Hamirpur, Kyelang, Kulu and the Spiti river[1085, 1096]), the Shiwalak Hills and the districts of Tehri, Kasauli,[1107] Ambala[1093] and Dehra Dun; the former Province of Kumaun[1113] (Almora and Naini Tal[1129]), the almost inaccessible Himalayan habitations in the State of Nepal;[1086, 1089] and the low-lying plains of Uttar Pradesh, including the Districts of Pilibhit, Bareilly,[1089, 1100] Bahraich, Gonda, Basti, and Gorakhpur, where Padrauna is especially noteworthy as a goitre centre[1128, 1129] South-east of Gorakhpur and not far from Patna lies the goitre district of Muzaffarpur studied by Sinha, Bose, Roychowdhury and Gyani.[1122, 1126] *Thus, there is an almost continuous stretch of goitrous* country filling the entire area between the Gogra river and the southern border of Nepal On a journey through Tibet, Harrer[1094] saw highly developed goitres at Drothang, the last stopping-place before Kyirong on the Tibetan side of the Himalayan barrier.

Still farther east the endemic continues across the river Gandak through Champaran and Purnea, it touches Darjeeling[1121] (also S R. Sen Gupta —personal communication, 1953) and the States of Sikkim and Bhutan[1088, 1123] Due south of this area, goitre has been recorded in East Pakistan at Dinajpur and Rangpur;[8] and in Assam there is an endemic of some intensity at Goalpara[1097] and throughout the Lushai and Naga Hills at places such as Tripura, Aijal, Imphal (Manipur) and Sibsagar[1090, 1119, 1121] (also A. K Mitra—personal communication, 1948)

Apart from this great northern endemic, goitre is by comparison not excessively acute elsewhere in India or Pakistan. Nevertheless, in Pakistan the disease is a distinct problem in the Multan and Montgomery areas of the west Punjab[1087, 1116] A recent epidemic (1955) in the Multan region was investigated by Murray et al[1118] Goitre has also been noted by McCarrison at Larkana on the lower Indus and it occurs sparingly on the Pakistan seaboard of Kutch[1104]

In the State of Rajasthan (formerly Rajputana) goitre is practically non-existent except in the Aravalli range and in the neighbourhood of the tributaries of the river Luni near Ajmer.[1104] South of the Luni and Aravalli area by about 300 miles, goitre is fairly common along the banks of the Narbada river, which flows westward to the gulf of Cambay between the Vindhya range on the north and the Satpura range on the south; in both these hilly regions the disease is not unknown.[1104]

The central Indian plateau of Madhya Pradesh is not conspicuously goitrous, but the malady is usually to be found in the neighbourhood of the southern tributaries of the Jumna and in the Jhansi and Lalitpur uplands where these rivers originate.[1104] On their goitre map of India, Megaw &

Gupta [1117] mark endemic centres between the Kaimur range and Jubbulpore; and there are reports of the disorder in the high country east of Jubbulpore affecting the Surguja and Ranchi districts of Chota Nagpur, and Sambalpur in Orissa (C Thomson—personal communications, 1951-52).

Throughout southern India goitre is found but sparingly. It has, however, been noted by Bodas & Deshmukh [1085] in and around the hill station of Mahableshwar in the Sahyadri ranges of the Western Ghats about 200 miles south-east of Bombay. McCarrison also saw goitre in this general area, at Bijapur, and farther south on the slopes and submontane tracts of the Western Ghats, particularly at Coimbatore and in the Nilgiri Hills. The Madras side and the Eastern Ghats are practically goitre-free with the exception perhaps of Arcot, where McCarrison records occurrences along the banks of the Cheyyar river in the vicinity of Arni [1104]

Thus, in summary, a competent cartoonist charged with the task of brushing-in the goitre areas on a map of the Indian peninsula would heavily underline the hollows under the entire length of the Himalayan " eyebrow ", lightly cover an irregular and fragmented area of secondary importance across the central plateau from West to East Pakistan, and merely touch some minor grey-spots in the Deccan and extreme south.

Degree of prevalence

In 1917, McCarrison [1105] estimated that the whole of India probably contained about five million goitrous people. He records that in some Himalayan villages 60% of infants still at breast were sufferers, and it was difficult to find a man, woman or child free from the disease. Thirty-five years later, Ramalingaswami,[1119] after reviewing all the statistical evidence available in the intervening period, reached the conclusion that the prevalence of endemic goitre in India had not changed appreciably in recent years and that McCarrison's estimate of five million affected persons was probably still valid in 1952 A later estimate (1959) puts the total at nine million [1098]

Hospital and dispensary returns [1097, 1119] give an idea of the relative severity of the disease in different parts of the Indian peninsula The greatest number of cases coming for treatment is encountered in the Dehra Dun, Gonda and Gorakhpur Districts of Uttar Pradesh (formerly the United Provinces) where an average of 100 000 persons presented themselves in 1940 and almost half that number in 1949 In Bihar, prevalence is about the same as in Uttar Pradesh, the most grossly affected district being Champaran. Sinha, Bose & Roychowdhury [1126] found an average rate of 11.7% among 8493 persons examined in the Muzaffarpur district of Bihar, with percentages rising to 50 and even 70 in one or two villages

The Punjab (particularly Kangra District), Bengal, and Assam (particularly Goalpara District) each yielded about 30 000 cases in 1940. In

Assam some 34 000 cases reported for treatment in 1949. The figures are as follows.

	1940	*1949*
Punjab (All)	30 000	—
Punjab (East)	—	10 508
Uttar Pradesh	100 000	44 723
Bihar	100 000	—
Bengal (All)	30 000	—
Bengal (West)	—	8 295
Assam	30 000	33 999
Madras	—	8 258
Bombay	—	926

Considering that only a small proportion of sufferers seek hospital treatment, the actual number of affected persons must be several times greater than the hospital returns. The results of some recent goitre surveys confirm this belief (see Table XVII)

TABLE XVII PREVALENCE OF GOITRE IN VARIOUS PARTS OF INDIA IN RECENT YEARS

Region	Prevalence of goitre (%)	Number of persons surveyed	Year of survey	Authority
Kashmir, Karakoram Mountains	90	—	1945	Allen-Mersh [1063]
Uttar Pradesh, Dehra Dun	32	554	1945	Ramalingaswami [1119]
Uttar Pradesh, Bareilly	26	133	1947	Lyall [1100]
East Punjab, Shiwalak Hills	32	5042	1952	Ramalingaswami [1119]
East Punjab, Shiwalak Hills	37	1337	1952	Ramalingaswami [1119]
Bihar, Purnea District	50	(3 villages)	1952	Ramalingaswami [1119]
Bihar, Ranchi District	70	563	1952	C Thomson (personal communication, 1952)
West Bengal, Darjeeling	67	8204	1953	Sen Gupta & Swarup [1124]

The annual report of the Public Health Commissioner with the Government of India for the year 1945 records a 70% goitre rate among schoolchildren in Ambala, East Punjab [1093] During their 1955 survey of 319 schoolchildren in Multan District, West Pakistan, Murray et al.[1118] found visible thyroid enlargement in 41 3% of boys and 72.3% of girls. The nutritional appraisal of the all-Pakistan armed forces conducted in 1956 by French et al ,[1092, 1130] revealed an overall thyroid enlargement rate of 6 8%; but among the men examined at Muzaffarabad the rate was no less than 31%. The Pathankot-Kangra-Gurdaspur region on the frontier between north-west

Pakistan and Kashmir is heavily goitrous, showing rates of from 30% to 90% in the areas of Kandi and Andhar. A stream running through this district has been called the Gilhari Khud ("goitre stream") since ancient times.[1098] In Sikkim State a goitre rate of 61 3% has been found at altitudes between 5000 and 6000 feet [1123]

Cretinism and deaf-mutism

Be they old or new, all descriptions of the goitre endemic in the heavily affected areas of northern India refer especially to the prevalence of cretinism, deaf-mutism and idiocy; these most tragic of the sequelae of goitre are as much a part of the endemic as the goitre itself According to Stott et al,[1129] affected villages in the Himalayan tract have an average goitre rate of about 40%, with some 4% of deaf-mutes. Stott and his colleagues have delved deeply into the incidence and distribution of deaf-mutism in the United Provinces (now Uttar Pradesh); their survey has not been bettered by anything published since. From various data they calculated that in 1921 there were 25 000 congenital deaf-mutes in the United Provinces alone, a figure substantially the same as that in 1911. In Stott's opinion the number of congenital deaf-mutes in the age-group 0-5 years is vastly underestimated because the parents of these unfortunate creatures hesitate to report their children as defective until all hope is lost, clinging as long as possible to the belief that speech and hearing are merely delayed.

Etiological factors

(1) *Pollution* McCarrison[1101, 1102] made a notable contribution to knowledge of the factors that influence thyroid enlargement when investigating the circumstances surrounding the occurrence of goitre in the nine neighbouring Himalayan villages collectively known as Gilgit Eight of these were situated one above the other on the same water-supply, which in its downward passage in surface channels to and through the successive villages became increasingly polluted by human and animal excreta The ninth village—Barmis—was located some distance apart and had its own water-supply, a spring of exceptional purity not subject to pollution. This village was free from goitre, but the disease prevailed in the other eight, with a rate which was least in the village at the highest level (11 8%) and gradually increased until it became 45 6% among the general population in Kashrote, the village at the foot

From these observations McCarrison concluded that the increasing intensity of goitre as one came down stream might be due to the obviously increasing impurity of the water-supply. To prove the point he administered to 35 volunteers, and to himself, a twice-daily drink containing a large quantity of the suspended matter filtered from the grossly polluted goitre-producing water issuing from Kashrote, the most severely affected Gilgit village In about a fortnight 10 of the 36 volunteers, one of them being

Assam some 34 000 cases reported for treatment in 1949. The figures are as follows:

	1940	*1949*
Punjab (All)	30 000	—
Punjab (East)	—	10 508
Uttar Pradesh	100 000	44 723
Bihar	100 000	—
Bengal (All)	30 000	—
Bengal (West)	—	8 295
Assam	30 000	33 999
Madras	—	8 258
Bombay	—	926

Considering that only a small proportion of sufferers seek hospital treatment, the actual number of affected persons must be several times greater than the hospital returns. The results of some recent goitre surveys confirm this belief (see Table XVII).

TABLE XVII PREVALENCE OF GOITRE IN VARIOUS PARTS OF INDIA IN RECENT YEARS

Region	Prevalence of goitre (%)	Number of persons surveyed	Year of survey	Authority
Kashmir, Karakoram Mountains	90	—	1945	Allen-Mersh [1093]
Uttar Pradesh, Dehra Dun	32	554	1945	Ramalingaswami [1119]
Uttar Pradesh, Bareilly	26	133	1947	Lyall [1108]
East Punjab, Shiwalak Hills	32	5042	1952	Ramalingaswami [1119]
East Punjab, Shiwalak Hills	37	1337	1952	Ramalingaswami [1119]
Bihar, Purnea District	50	(3 villages)	1952	Ramalingaswami [1119]
Bihar, Ranchi District	70	563	1952	C Thomson (personal communication, 1952)
West Bengal, Darjeeling	67	8204	1953	Sen Gupta & Swarup [1124]

The annual report of the Public Health Commissioner with the Government of India for the year 1945 records a 70% goitre rate among schoolchildren in Ambala, East Punjab [1093] During their 1955 survey of 319 schoolchildren in Multan District, West Pakistan, Murray et al [1118] found visible thyroid enlargement in 41 3% of boys and 72 3% of girls. The nutritional appraisal of the all-Pakistan armed forces conducted in 1956 by French et al.,[1092, 1130] revealed an overall thyroid enlargement rate of 6.8%; but among the men examined at Muzaffarabad the rate was no less than 31%. The Pathankot-Kangra-Gurdaspur region on the frontier between north-west

limy smell, and above all by the fact that it remains warm in all seasons whereas good (non-goitrogenic) water invariably keeps cool.

(3) *Poverty and faulty diet.* Others among the many who have observed goitre in India point to poverty and insufficient and imperfect dietary as the main conditions in which the disease originates Bramley[1086] noticed this in Nepal and Tibet in 1833; Macnamara[1116] refers to it; and so do McCarrison & Madhava,[1109] who, in discussing the genesis of goitre in India, attach much importance to faulty and unbalanced diets. C. Thomson (personal communications, 1951-52) links poverty with the goitres seen in villages below the Ranchi plateau in Bihar where a cheap dietary composed largely of sweet potatoes is used extensively instead of cereals Stott & Gupta[1128] correlate the distribution of goitre in the Padrauna *tehsil* of Gorakhpur with the distribution of *bhat* and *bangar* soils. Broadly speaking, the superendemic areas are confined to the sandy *bhat* soils, which yield food produce of low quality Villages on *bangar* soil, which yields high quality food, are generally goitre-free

(4) *Iodine deficiency* Early chemical investigations by McCarrison et al[1112] provide no evidence that in Himalayan India the incidence of endemic goitre is in inverse ratio to the iodine content of soil and water In the heart of the endemic zone, as well as in the Himalayan foothills, two places adjacent to one another may have approximately the same amount of iodine in their soils yet goitre may be prevalent in one and not in the other. Similarly, one locality may have a water supply containing an appreciable amount of iodine and yet be a focus of endemic goitre, while another locality may have a water supply containing less iodine and yet be free from endemic goitre This is because the iodine level in Himalayan soils and waters is not the determining factor in goitre causation here As has already been mentioned, bacteriological impurity in water is the essential goitrogenic agent, although it is true that this effect may be mitigated and controlled in proportion to the quantity of iodine present in the water.

On the other hand, Murray et al[1118] find that the chief factor determining the occurrence of goitre in the Multan area of West Pakistan is the iodine content of the local drinking-water. Eight representative samples used by goitrous people in this region were compared in respect of iodine content with control samples from Kasur, about 200 miles distant, where goitre is unknown. The eight Multan waters had an average iodine content of 3 6 μg per litre usually associated with a high degree of hardness By contrast, water from the non-goitre district of Kasur had an iodine content of 10 8 μg per litre

Goitre has long been known in the Multan region of West Pakistan Macnamara[1116] described it there in 1880; Chaudhri[1087] noted a rate of 60% in the villages of the Kabirwala *tehsil* in 1929, and Wilson[1131] referred to it in 1941 in connexion with her fluorosis investigations in that area According

McCarrison himself, developed noticeable thyroid enlargement; 5 had transitory swellings and 21 were unaffected. Concurrently, 31 other young men consumed, in the same circumstances, the same suspended matter after it had been boiled. None developed goitre.

These early experiments are mentioned here because they offer the *first experimental proof* of an assertion constantly recurring throughout the goitre literature of primitive countries—namely, that excessive amounts of organic material in water, whether the actual bacteria themselves or some toxin produced by them, can exercise a goitrogenic effect and thus raise the bodily demand for iodine in the same way as can the excessive concentration in drinking-water of an inorganic chemical constituent such as calcium.

Confirmation of this point of view is afforded by McCarrison's later experience in a boarding-school at Sanawar, not far from Kasauli in the outer Himalayas.[1107] Here, goitre had persisted for many years and at the time of McCarrison's inquiry was affecting no less than 66% of girls over 15 years of age. Investigation showed that the school water-supply—a spring—was subject to bacterial pollution from human and animal excreta. A new and clean supply was introduced; within a few years goitre had entirely disappeared from the school.

In this connexion one recalls the modern thesis of Hettche,[1085] who concludes from his epidemiological and etiological study of goitre as revealed in one hundred years of research, that the disease is caused by an injurious substance of the urochrome group occurring in contaminated water-supplies. The toxic agent is said to bind copper in the serum and can be used to produce goitre experimentally in animals, but the production of goitre may be prevented by simultaneous administration of iodine. McCarrison also found that goitres developing spontaneously in well-fed experimental animals confined in dirty cages could be prevented by increasing the consumption of iodine proportionately to the unhygienic conditions under which the animals were living.

(2) *Lime-rich waters and soils.* The frequent association of goitre with limestone rocks and with drinking-water rich in lime has been noted from earliest times. McClelland's[1114] extensive medico-topographical studies in places as far apart as Bengal and the North-West Provinces led him to the conclusion, published in 1835, that magnesian limestone formations were primarily responsible for the propagation of goitre in India. There is little new under the sun, for, one hundred years later, Stott and his colleagues[1129] advanced very much the same view and pointed to a direct correspondence between the distribution of goitre in the United Provinces and drinking-waters and soils of high calcium content. Moreover, many villagers in this area know that it is a "chuna" water containing a large excess of lime and coming from limestone rocks that is the peculiar cause of goitre. They recognize it by its hardness, heavy consistency, astringent taste,

tive need to begin fighting endemic goitre at once, but also because it is not easy to persuade people in the endemic areas, who have been accustomed to crude crystalline salt for centuries, to change over [illegible] to refined salt.

To [illegible]
occ[illegible] [illegible] ...ungal of India, iodization
of s[illegible] [illegible] preferred Experiments have already been [illegible]
by C Thomson (personal comm[illegible]
d[illegible]
[illegible]
t[illegible]
formed a [illegible] ...altan-
kot-Kang[illegible] [illegible] ...Punjab.[1096] Results are awaited
with inten... interest

Ceylon

Pendant on the Indian subcontinent hangs the pear-shaped island of Ceylon, approximately the size of Holland and Belgium combined, and inhabited by about seven million people. The south-west-central area, where population density is greatest, is mountainous, wet, and goitrous, the rest of the country to the east and north is flat, dry, and comparatively goitre-free. Heavy rainfall and high temperatures in the south-west region where goitre chiefly occurs have led to intense [illegible] ...il
leaching of the ancient [illegible]
giving rise to later[illegible] ... the degree of leaching
Waters throughout [illegible] ...and are soft, and those from the highly leached goitrous areas in the south-west have a low iodine content. These are the essentials

Greenwald,[892, 1132] who has probed into the history of goitre in many countries, finds only three original mentions of the disease in Ceylon prior to Wilson's [1133, 1134] survey of 1950, one in 1843, one in 1849 and one in 1894, these all relate merely to occasional occurrences in the Galle district of the extreme south-west From this he concludes that goitre was not common in Ceylon until quite recent times

In the course of nutrition surveys carried out by workers of the Medical Research Institute at Colombo during the years 1947-49 it was reported that goitre was endemic in certain rural parts of the island. Early in 1950, Wilson [1133, 1134] was asked by the World Health Organization on behalf of the Ceylon Government to ascertain whether the amount of goitre reported in these surveys constituted a serious public health menace She examined 722 Ceylonese children and adolescents—317 boys and 405 girls—attending rural schools in ten different parts of the island, six in the wet region of the south-west and four in the dry region of the north The results are shown in Table XVIII

to recent reports[1118] medical observers are convinced that goitre has greatly increased in the Multan area and in West Pakistan generally since 1947 when, owing to the partition of Pakistan and India, unusual movements of populations have taken place and additional water-pumps have had to be installed on old sites to cope with the increased requirements. Apparently the new water-supplies do not always have an adequate iodine content.

Animal goitre in India

Bramley[1088] records that during his sojourn in Nepal, where goitre is notorious among men, women and children of all ages, it was by no means uncommon to find animals such as the buffalo, goat, sheep, and dog similarly affected. On one occasion he saw a goat bring forth a kid with a goitre as large as its head Animal goitre is also specifically mentioned as occurring among dogs, cats and birds in the super-endemic areas of Gonda and Gorakhpur in Uttar Pradesh A. K Mitra (personal communication, 1948) gives an interesting account of goitre among calves in the Subsagar district of Assam, an area where human goitre also prevails. Thyroid glands from goats and sheep slaughtered at Bareilly, a district of human goitre, were examined (1959) by Dutt & Kehar.[1089] About 10% of the goats were goitrous, but no thyroid enlargement was seen among the sheep

McCarrison,[9] on the other hand, rarely came across goitre in animals. In the course of ten years' residence in the Chitral and Gilgit districts he saw only two cases in dogs, one in a horse, and one in a goat. Altogether McCarrison examined 116 mules, 101 dogs, 150 cows, 100 sheep and goats and 101 ponies belonging to the villagers of Gilgit, but did not encounter a single case among these 568 animals. No history of goitre in domestic animals was obtained by Murray et al [1118] during their survey in the Multan region of West Pakistan.

Preventive measures

Despite the etiological complexity of the Indian goitre endemic it is not denied, even by those who show that the cause of goitre in India is impure water or excessive calcium intake rather than a primary iodine deficiency, that the easiest and cheapest way of preventing the disease is to provide the necessary supplementary requirement of iodine in iodized salt. Here, as Ramalingaswami points out, India is confronted with a difficult problem.

Except for a small quantity of rock salt mined at Mandi in Himachal Pradesh, the bulk of the salt produced in India is a coarse crystalline product obtained by solar evaporation of brine About three-quarters of this is made up of sea salt and the remainder is obtained from inland salt lakes Efforts are being made by the Salt Expert Committee of the Government of India to improve permanently the quality of Indian salt, but in the meantime ways are being explored of iodizing the currently used crude salt as uniformly as possible This is important not only because of the impera-

to subsist on restricted dietaries inadequate in protein and supplemented with local vegetable foods not largely consumed in normal times. Wilson conceives it possible [1134] that insufficient intake of the right kind of protein, and an increased intake of anti-thyroid material ingested from the unusual foods consumed during the war might be sufficient to interfere with iodine metabolism and hormone synthesis and so cause thyroid enlargement. There is, however, no proof of this

As a goitre-preventive measure, potassium iodide tablets were distributed in some areas as a result of Wilson's survey and recommendations, but there is little sign that the preventive programme continues to be pursued with vigour and determination.

Burma

Goitre is prevalent in the mountainous parts of Burma, particularly throughout the Chin Hills in the west of the country, the Kachin Hills in the north, and the Shan States on the east The western and northern goitre areas are contiguous with the endemics covering the Lushai and Naga Hills of eastern Assam

Statistics gathered by Raymond [1136] from groups of villages in the Chin country show that the disease is commoner among children than among adults, but the adult goitres are much larger and frequently give rise to serious pressure symptoms Incidence is higher in females than in males and is always greatest at puberty and pregnancy. Water-supplies are singularly pure and free from faecal contamination, and therefore are not incriminated, but dietary deficiency of vitamin A is notorious, and Raymond regards this as the most important single goitrogenic factor operating among the Chin Hills people

On the north and east, where Burma abuts on China, goitre rates are exceedingly high in the Myitkyina area, also around Bhamo, Namkham and Shwegu in the Northern Shan States, and on the Burma-China road in the neighbourhood of Lashio and eastwards towards the Salween river.[1129] Secluded valleys in the Shan States are particularly affected, according to Robertson,[1204, 1206] and the disease seems often to be confined to certain tribes Seagrave [1137] mentions that in the limestone hills of the Namkham area at least half the population suffer from goitre

An exceptionally large number of cretins and deaf-mutes are seen in the Burmese goitre areas [1129, 1135] Among the Kachins who inhabit the valleys and steep hill-sides along the north and north-east frontiers the enormous rate of 10 per 1000 is recorded by Stott et al [1129] The Kachin people drink water from hill streams impregnated with lime and customarily eat large quantities of lime in powdered form Stott and his colleagues believe that this peculiar habit is in large measure responsible for causing goitre among these northern Burmese peoples

TABLE XVIII PREVALENCE OF GOITRE AMONG CEYLONESE CHILDREN AND ADOLESCENTS IN TEN DIFFERENT PARTS OF CEYLON

Situation of villages	Boys		Girls		Iodine content of water (µg per litre)
	number examined	percentage with goitre	number examined	percentage with goitre	
Wet region					
1 On coastal strip, inland	20	15 0	50	38 0	2.2
2 On sea coast	50	18 0	50	40 0	5 3
3 On coastal strip, inland	—	—	50	22 0	—
4 On foothills, inland	45	13 3	26	23 1	—
5 On hills, inland	50	6 0	50	56 0	2 7
6 At 5000 feet, inland	27	11 1	30	40 0	1 4
Total	192	12 5	256	37 5	
Dry region					
7 On sea coast	—	—	50	6 0	—
8 On coastal lagoon	50	Nil	30	6 7	—
9 On Jaffna peninsula	50	Nil	50	12 0	6 6
10 On plateau, inland	25	Nil	19	5 3	61 0
Total	125	Nil	149	8 0	

In general, prevalence is highest in the section of the country where rainfall is highest This covers the Central, Western and Sabaragamuwa Provinces, which include the coastal strip between Colombo and Galle The drier eastern and northern provinces of the island are not seriously affected, although a rate of 12% was found by Wilson among girls in a school on the Jaffna peninsula in the extreme north.

As is usual, girls and women of child-bearing age are the chief victims Among boys incidence is only moderate and few goitres are seen in men. Toxic symptoms are rare in Ceylon and no cases of cretinism or deaf-mutism are recorded. Animal goitre is also unknown

Drinking-waters are generally soft and therefore the hard-water factor cannot be incriminated; but some waters, notably in the coastal villages numbered 1 and 2 in Table XVIII gave evidence of faecal and bacterial contamination which could decrease the amount of available iodine. It is evident that waters from the wet goitrous regions are much less rich in iodine than those from the dry non-goitrous localities

Adverse economic circumstances and shortage of rice owing to imported supplies from Burma having been cut off during the 1939-45 war have in recent years obliged many Ceylonese communities, particularly in the south,

prabang into the Yunnan Province of China; (2) the upland area of North Viet Nam (formerly Tonking) lying to the north of Tuyenquang, and (3) the Mekong delta of South Viet Nam (formerly Cochin-China) with Cantho as its centre Apparently goitre does not occur—or only sparingly—in the great Annam mountain chain curving in a half-circle through Viet Nam from Kamkeut in the north to Saigon in the south Lower and middle Laos, and the plains of Cambodia (with the exception of Cochin-China in the very south), are goitre-free. It may also be mentioned here that goitre is known to occur in the Kingdom of Thailand on the west of Indo-China, for the most part a low-lying country;[1381] two recent unpublished accounts are those of Ramalingaswami[1139] and Klerks.[1134]

The authority on the first of these Indo-Chinese goitre areas is Jeanselme[1142] who, when journeying up the Mekong river from the south, first saw "*neang*" (the name by which goitre is known among the people of northern Laos) in the country beyond Vientiane As he penetrated further into this calcareous mountain region, Jeanselme observed that the disease became more and more pronounced At Luangprabang, a sizeable town situated on the confluence of the Mekong and its tributary the Nam Khan, he saw some enormous tumours, mostly among women

Somewhat to the east, goitre is prevalent along the Tranninh river and in the region between Borikan and Xiengkhouang where about half the population is affected North of Luangprabang, up the river Nam Hu, the disease is of common occurrence on both banks as far as the village of Moungngoi, but beyond this point in the direction of Laichau along the valley of the Nam Ngoua, a tributary of the Nam Hu, prevalence appears to diminish, and in the riparian villages of the Black River (Song Bo), on which Laichau is situated, goitres are neither frequent nor voluminous, even among women

The second goitre region in Indo-China lies across the Red River (Song Koi) to the north-east of the first in the northern part of Tonking (upper North Viet Nam) It comprises the area between Tuyenquang and Kaobang, including Chem Hoa Chow and the steep escarpments and gorges through which the Song Gam and the river Claire flow south to join the Red River near Tuyenquang Its northern edge touches the Chinese Province of Kwangsi

Various writers have called attention to goitre in this section of Indo-China—notably, Clavel in 1890 (Tuyenquang), Sadoul in 1890 (upper Black River), Billet[1141] in 1896 (Upper Kaobang), Jeanselme[1142] in 1910, Le Roy des Barres in 1923, Cloitre[1069] in 1930, and Tran Kiem Phan in 1937 (see Leuret[1113]) Only the northern hilly parts of the area beyond Tuyenquang are affected; goitre does not exist on the low-lying swampy delta around Hanoi where rice is grown Jeanselme examined 377 prisoners (283 men and 94 women) from delta provinces and did not find a single case Upstream on the Red River, however, from Ta Than as far as Man Hao

Thailand

Goitre is prevalent in the north and north-east of Thailand. Towards the end of November 1955 and continuing through January 1956, Ramalingaswami [1139] surveyed the region and found overall rates of 58% in the northern Provinces of Chiengmai and Chiengrai, a high percentage of the goitres being pathological. By contrast, the north-eastern Provinces of Ubol and Udorn showed fewer cases (21% and 15% respectively), the vast majority being mild. As the disease is so highly endemic in Chiengmai and Chiengrai, Ramalingaswami recommended the institution of a control programme with iodized salt and the collection of additional survey data in the northern Provinces

Klerks [1138] who was assigned to this programme during the two years 1957-1958 assessed the situation in boys and girls of 7 to 12 years of age as shown in Table XIX

TABLE XIX PREVALENCE OF GOITRE AMONG BOYS AND GIRLS IN THAILAND

Province	Boys		Girls	
	number examined	percentage with goitre	number examined	percentage with goitre
Chiengmai	1013	19 7	945	27 5
Uttaradit	300	40 3	281	50 9
Prae	869	37.3	661	41 7
Lampang	200	36 0	216	46 3
Chiengrai	474	43 5	513	54 8
Total	2856	32 3	2816	40 8

The fact that there is no governmental salt monopoly in Thailand is the greatest obstacle to a programme of salt-iodization. Even provincially, or in limited local areas, such a measure would at present be difficult to control because of the large number of individual retailers who draw their supplies from all sorts of different sources. Moreover, some communities do not use much salt but rely for seasoning on fish sauce, not a suitable medium into which to introduce iodide or iodate Every endeavour is being made to overcome this problem; one suggestion is that in the goitre areas iodate might be incorporated in the vitaminized premix already being added to polished rice used in beriberi areas (Van Eekelen [1140]).

Indo-China (Cambodia, Laos and Viet Nam)

Reports of goitre come from three parts of Indo-China: (1) the mountainous region extending northwards from Vientiane through Luang-

14 years of age and found 48 with visible thyroid enlargement. Three other districts in Upper Perak—the *kampongs* of Ulu Kendrong, Klian Malau, and Ulu Jepai—also show high rates, especially among women.

Goitre is extremely common in the central states of the country—notably, in and around Kuala Betis and along the Nenggiri river in Kelantan; in the basins of the rivers Aring, Trengganu and Tembeling in Trengganu; and especially in the Ulu Jelai area of Pahang extending from the Cameron Highlands south-eastwards across the Telom Jelai-Kechil watershed as far as Kuala Lipis Goitres among trout introduced into mountain streams in the Cameron Highlands have been reported by Le Mare,[1144] who also mentions the prevalence of the disease among the human population in that locality

Other goitre centres in Malaya are found along the western slopes of the main mountain chain—for example, at Ulu Luit and Ulu Langat in Selangor, and at Ulu Beranang in Negri Sembilan. In the *kampongs* situated near Alor Gajah some 10 to 20 miles from the Malaccan coast prevalence is much less than in central Malaya, and on the extreme south coast of Johore and in Singapore goitre is practically non-existent.

Polunin's data are summarized in Table XX In a total of 1328 people —618 Malays and 710 aborigines—dwelling in the inland parts of Pahang and Upper Perak, and on the western slopes of the central mountain chain, the goitre rate was 39.5% for the Malays and 40 8% for the aborigines. The disease is not confined to any particular geological formation, indeed, the only goitre-free area is one where limestone predominates

Malayan waters are usually soft and their iodine content is exceedingly low. Seven samples drawn from rivers draining inland areas where goitre incidence is high gave values from 0 2 μg to 0 6 μg of iodine per litre Iodine deficiency is therefore considered to be the primary cause of goitre in Malaya, calcium excess does not enter into the problem.

Indonesia

Centres of endemic goitre are found throughout the whole length of the Indonesian archipelago, from Sumatra in the west to Timor in the east. The following summary of affected localities is compiled from the papers of Pfister,[1160-1164] Donath,[1150] van Bommel,[1147] Eerland,[1151-1153] Eerland, Noosten & Vos,[1154] Noosten,[1159] Elsbach,[1155] van Gulik,[1157] Simons,[1167] and others (see bibliography)

Sumatra

The northern and central volcanic regions inhabited by the Batak people, including the high plains of Groot-Atjeh; the plateau of Gajo-Loeos; the Lokŏp valley, the Alas valley, the east coastal plains of Bindjai and Deli in the *dusun* of Upper Langkat; the Siantar Uluan country; the

goitre is endemic on both banks It is here that the upper Viet Nam endemic passes from Indo-China into Yunnan (see page 176).

The third, less well recognized, zone of goitre in Indo-China is the Bassac strip of Cochin-China in the extreme south which has recently been stigmatized as goitrous for the first time by Leuret.[1143] It consists of the seven Trans-Bassac Provinces—Hatien and Rachgia on the Gulf of Siam, Chaudoc, Longxuyen, Cantho and Soctrang along the Bassac, and Bacheu on the shores of the China Sea—and the two Cis-Bassac Provinces of Sadec and Vinhlongh

This vast region is entirely alluvial, semi-liquid, semi-solid, traversed by thousands of canals and small channels Hot and humid, it lies practically at sea level with no irregularities other than the low dykes and road bridges of the rice fields. Springs and wells are unknown, drinking-water is provided by the rains of the winter and summer monsoon seasons, and by the canals at all seasons No systematic goitre survey has been carried out in the area, but Leuret [1143] considers it significant that he was called upon to operate on 29 goitres in a continuous period of 22 months, especially in a region where the people do not characteristically appeal to western medicine until they have exhausted the resources of the witch-doctor Moreover, even when patients must eventually have recourse to the modern medical and surgical clinics of the west, they display a maximum of resistance in regard to surgery. This is more particularly true of goitre, which is regarded at most as a disfigurement to be borne without complaint. Under these circumstances, 29 goitres operated upon by one surgeon within 22 months in a region not ordinarily deserving the appellation " endemic " must denote a relatively high general incidence. Confirmation of this belief was forthcoming from Leuret's second series of surgical cases in which there were 12 goitres out of 93 operations of all kinds

Malaya

Polunin [1146] has gathered together all the available information on goitre in Malaya and has himself considerably added to it His maps are models of what goitre maps should be. Visible thyroid glands are common in most of the undeveloped mountainous inland areas, the over-all rate being about 40%. By comparison, the rate among communities near the sea is only between 1% and 2%.

In the northern third of the country, the areas chiefly affected are the hills and valleys of Kedah and Upper Perak A health survey of the State of Kedah in 1935-36 revealed 131 cases of goitre in the districts of Sok and Jeneri On the banks of the Chapar, a tributary of the Sok river, there were two *kampongs* (Banggol Batu and Banggol Berangan) where all the inhabi-

the

over

14 years of age and found 48 with visible thyroid enlargement Three other districts in Upper Perak—the *kampongs* of Ulu Kendrong, Klian Malau, and Ulu Jepai—also show high rates, especially among women.

Goitre is extremely common in the central states of the country—notably, in and around Kuala Betis and along the Nenggiri river in Kelantan; in the basins of the rivers Aring, Trengganu and Tembeling in Trengganu; and especially in the Ulu Jelai area of Pahang extending from the Cameron Highlands south-eastwards across the Telom Jelai-Kechil watershed as far as Kuala Lipis Goitres among trout introduced into mountain streams in the Cameron Highlands have been reported by Le Mare,[1141] who also mentions the prevalence of the disease among the human population in that locality

Other goitre centres in Malaya are found along the western slopes of the main mountain chain—for example, at Ulu Luit and Ulu Langat in Selangor, and at Ulu Beranang in Negri Sembilan. In the *kampongs* situated near Alor Gajah some 10 to 20 miles from the Malaccan coast prevalence is much less than in central Malaya, and on the extreme south coast of Johore and in Singapore goitre is practically non-existent

Polunin's data are summarized in Table XX. In a total of 1328 people —618 Malays and 710 aborigines—dwelling in the inland parts of Pahang and Upper Perak, and on the western slopes of the central mountain chain, the goitre rate was 39 5% for the Malays and 40 8% for the aborigines The disease is not confined to any particular geological formation; indeed, the only goitre-free area is one where limestone predominates.

Malayan waters are usually soft and their iodine content is exceedingly low Seven samples drawn from rivers draining inland areas where goitre incidence is high gave values from 0 2 μg to 0 6 μg of iodine per litre. Iodine deficiency is therefore considered to be the primary cause of goitre in Malaya; calcium excess does not enter into the problem.

Indonesia

Centres of endemic goitre are found throughout the whole length of the Indonesian archipelago, from Sumatra in the west to Timor in the east. The following summary of affected localities is compiled from the papers of Pfister,[1160-1164] Donath,[1150] van Bommel,[1147] Eerland,[1151-1153] Eerland, Noosten & Vos,[1154] Noosten,[1159] Elsbach,[1155] van Gulik,[1157] Simons,[1167] and others (see bibliography)

Sumatra

The northern and central volcanic regions inhabited by the Batak people, including the high plains of Groot-Atjeh; the plateau of Gajo-Loeos; the Lokop valley, the Alas valley; the east coastal plains of Bindjai and Deli in the *dusun* of Upper Langkat; the Siantar Uluan country; the

TABLE XX PREVALENCE OF GOITRE IN RELATION TO GEOLOGICAL FORMATION IN MALAYA

Locality and race	*Geology*	Number of people examined			Percentage with goitre		
		males	females	total	males	females	total
Pahang, Ulu Jelai							
Aborigines	granite	185	161	346	39	67	52
Malays	limestone	230	190	420	22	52	36
Upper Perak							
Aborigines	quartz porphyry, limestone, granite	87	76	163	6	43	23
Malays		53	50	103	21	74	48
Western slopes of main mountain chain *							
Aborigines	quartz porphyry and granite	117	84	201	21	55	35
Malays		50	45	95	38	53	47
Total		722	606	1328	25	57	40
Coastal regions of Johore							
Aborigines	alluvium on granite	46	22	68	2·1	Nil	1·4
Malays		76	40	116	Nil	2·5	0·8
Total		122	62	184	0·8	1·6	1·1
Alor Gajah district, Negri Sembilan							
—	limestone	31	42	73	6	17	12

* From Kuala Chenka in Perak through Selangor and Negri Sembilan to Lenek in Johore

mountain region of Sinaboeng and Sibajak; the whole area around Lake Toba, including the peninsula of Samosir, Mandailing; the slopes of Mount Ophir, the country surrounding Lake Koto as far as Padang-Pandjang on the west, and Solok and Padang on the south. At the southern end of Sumatra, goitre is prevalent along the Barisan mountains, particularly in the sub-department of Lebong in the area of the river Ketuan; also at Moeara-Aman and Benkoelan, and in the valleys of the rivers Batang Hari and Komering

As far back as 1883, Marsden[1158] *wrote in his history of Sumatra that* " the natives of the hills through the whole extent of the island, are subject to those monstrous wens from the throat, which have been observed of the [illegible] of other mountainous districts in Europe ". Tod [illegible] high, amounting in some places to mor [illegible] in men Cretinism and deaf-mutism are common.

Particularly goitrous are the inaccessible mountain tracts occupied by the Batak peoples in the north—Gajo-Loeös (Atjeh), the Alas valley, and all the country surrounding Lake Toba southwards to Padang and Solok The whole region has a volcanic geology and parts of it are almost entirely covered with vast layers of light tuffaceous rocks and soils. According to Elsbach[1155] the population of the Gajo-Loeös live in a perpetual state of iodine deficiency. Drinking-waters contain only between 0.6 μg and 2.8 μg of iodine per litre, and Alasland agricultural soils analysed by von Fellenberg for van Bommel[1147] showed an iodine content no higher than the lowest values recorded for soils from European goitrous areas

Java

The chief endemic foci in Java are the Residency of Kedoe; the Dieng plateau; the villages around Wonosobo, Garoeng and Magelang; the Tengger mountains; and, above all, Kediri, a district in the centre of the country south-west of Soerabaja dominated by the two volcanoes Wilis and Keloet South-east of the Residency of Kediri, near Blitar, is Penataran, where goitre is said to be endemic; the disease also occurs in the remote limestone wilderness of Lodojo, and in a narrow strip to the south of the Brantas river

The prevalence of "gondok", as goitre is called in Java, is normally about 60% among schoolchildren in Kediri, but may often be 80% and in some villages has been known to reach even 100% Eerland,[1152] who has studied this area closely, recorded 126 cretins, a much larger number of cretinoids, and nearly 2000 deaf-mutes. He says that the normal thyroid gland of Javanese peoples living in non-goitrous areas is smaller than that of the European and averages 11 9 g The so-called "normal" gland in the goitrous Kediri district has an average weight of 52 g in males and 57 g in females In a random sample of 249 goitrous subjects from Kediri, 67 had goitres weighing over 500 g (1 lb) The two largest weighed respectively 2850 and 2930 g, or between 6 and 6 5 lb. Toxic goitre is rare in Java.

Superstitions regarding the cause of goitre include belief in "goitre images" Near Penataran close to the source of the Soemberdandang stands a Hindu goitre image with the head of an elephant. People believe that at certain times this image pours water from its trunk into the nearby wells and streams, and that anyone drinking this water will inevitably contract goitre.

Bali

Expert studies of ancient Javanese medical texts written on copper and on lontar leaf indicate that goitre has afflicted the island of Bali for perhaps ten centuries With certainty the disease has been known there for a hundred years, it is mentioned by almost every writer on goitre in the Dutch East Indies since 1856

The plateau of Tjatoer in the north-east section of the island is the major seat of the endemic. Anyone who has witnessed market-day at Kintamani when people come together from the whole plateau will be convinced of this at a glance. Moreover the area provides another striking example of the extraordinary selectivity of the goitre noxa At the end of a path leading off the main road between Singaradja and Kintamani lie two villages—Lampoe and Tjatoer—quite different in character although only a few hundred yards apart Lampoe is the home of about 100 Chinese traders, established there for three generations and much intermingled by marriage with the native Balinese Food is varied, water is boiled before use, there is not a single case of goitre Tjatoer, on the other hand, contains some 700 pure Balinese belonging exclusively to the Bali Aga race, the original inhabitants of the island These people lead quite different lives from their immigrant Chinese neighbours Poverty-stricken, unwashed, and commercially undeveloped, they subsist on a monotonous diet of maize and rice; water is drunk unboiled from a goitrogenic spring cursed by Dewa Belanga (see below) Goitre is very prevalent in Tjatoer.

Noosten,[1159] to whose exhaustive description of goitre in Bali we are indebted for the foregoing, also gives an intensely interesting account of the traditional beliefs concerning the infliction of thyroid disease by the goitre goddesses Dewa Ajoe Bengkala and Dewa Belanga, and of the lengthy and involved festivals (*slametans*) celebrated, often at great cost, to placate these ill-disposed deities and exorcize their evil spirits Noosten also details some of the complex mediaeval concoctions prescribed as remedies for goitre in Bali, and gives examples of the secret *incantations*, or *mantras*, recited when these medicines are administered He illustrates, too, some of the magic figures and devices scratched or engraved on the cooking vessels in which the recipes are prepared These primitive signs are supposed to enhance the magic power of the drug

From all his patient collection of facts and folklore about goitre in Bali, Noosten concludes that preoccupation with the disease, and in fact the whole goitre concept, is deeply rooted in the Balinese people No better evidence of this can be found than in the words uttered when a Balinese wishes emphatically to protest his innocence: "*Apang gondong tiang toesing nawang*", which means "May I get goitre if I know anything about it"

Celebes and Timor

Goitre occurs at Madjene and at Maros on the west coast of Celebes (Donath [1150] and Noosten [1159]). Two other centres are marked on Noosten's map of this oddly shaped island, one almost at the tip of the northern arm in the neighbourhood of Kotamobagoe and the other near Masamba in central Celebes due north of the Gulf of Bone.

In Portuguese Timor, goitre is known throughout the north-east section of the island between Manatuto on the north coast and Kailaco on the south (Noosten [1159]) Most modern statistics from this region are those of Fraga de Azevedo, Franco Gândara & Pedroso Ferreira [1158] whose survey (1958) revealed an average rate of 10% in the two upland localities of Laclubar and Fato-Berlio. The fundamental cause of goitre in this area appears to be lack of sufficient iodine in the water supply, coupled with a diet predominantly carbohydrate and low in fat and protein.

Indonesian Borneo

In central and south-eastern Borneo goitre is reported [1159] to occur at the following places (1) along the Melawi valley, in the neighbourhood of Sekajam, and in the Sipoeak river area, (2) on the Apo-Kajan plateau and in the Kotei or Mahakam river basin to the north-centre of the country; (3) on the banks of the Barito river, and at Meratoes and Martapoera in the south-east of the country. Details of incidence and other features of the endemic in central Borneo are lacking.

Goitre prophylaxis in Indonesia

Preventive measures were first introduced in 1927, when iodized salt (1 : 200 000) was distributed throughout the Dieng plateau and Tengger area of Java. By 1930 prophylaxis had been extended to the Gajo and Alas regions of Sumatra, and in 1933 the Kediri Residency of Java followed suit [1150, 1159, 1166] Writing in 1939, Simons [1167] pronounces the step justified by the favourable results and makes a plea for its extension He affirms that iodized salt is completely harmless

At the time these preventive measures were introduced, salt was manufactured under monopoly and in block form only at the salt works on the island of Madoera off the north-east of Java The method of iodization is unique In view of the high temperature to which the salt is exposed in the brick-making machine, it is essential to avoid incorporating iodine in the salt before it passes into the machine, otherwise iodine will be lost in [illegible]

per ml, is poured from a small spoon into a hollow on the top of each brick, and by capillary action spreads evenly throughout the entire brick In this way 3 3 mg of iodide are absorbed by each 600-g brick, giving an iodization level of 1 in 200 000 (Donath [1150])

Around the year 1939 or 1940, the level of iodization was raised from 1 in 200 000 to 1 in 100 000, and experiments were made by Van Veen [1169] (also personal communication, 1950) in the goitrous Kintamani plateau of Bali to see whether the crude sea salt used by the Balinese population could be iodized in granulated instead of brick form without loss of the

The plateau of Tjatoer in the north-east section of the island is the major seat of the endemic Anyone who has witnessed market-day at Kintamani when people come together from the whole plateau will be convinced of this at a glance. Moreover the area provides another striking example of the extraordinary selectivity of the goitre noxa. At the end of a path leading off the main road between Singaradja and Kintamani lie two villages—Lampoe and Tjatoer—quite different in character although only a few hundred yards apart Lampoe is the home of about 100 Chinese traders, established there for three generations and much intermingled by marriage with the native Balinese Food is varied; water is boiled before use, there is not a single case of goitre Tjatoer, on the other hand, contains *some 700 pure Balinese belonging exclusively to the Bali Aga race, the original* inhabitants of the island. These people lead quite different lives from their immigrant Chinese neighbours Poverty-stricken, unwashed, and commercially undeveloped, they subsist on a monotonous diet of maize and rice; water is drunk unboiled from a goitrogenic spring cursed by Dewa Belanga (see below) Goitre is very prevalent in Tjatoer.

Noosten,[1159] to whose exhaustive description of goitre in Bali we are indebted for the foregoing, also gives an intensely interesting account of the traditional beliefs concerning the infliction of thyroid disease by the goitre goddesses Dewa Ajoe Bengkala and Dewa Belanga, and of the lengthy and involved festivals (*slametans*) celebrated, often at great cost, to placate these ill-disposed deities and exorcize their evil spirits. Noosten also details some of the complex mediaeval concoctions prescribed as remedies for goitre in Bali, and gives examples of the secret incantations, or *mantras*, recited when these medicines are administered. He illustrates, too, some of the magic figures and devices scratched or engraved on the cooking vessels in which the recipes are prepared. These primitive signs are supposed to enhance the magic power of the drug

From all his patient collection of facts and folklore about goitre in *Bali, Noosten concludes that preoccupation with the disease*, and in fact the whole goitre concept, is deeply rooted in the Balinese people No better evidence of this can be found than in the words uttered when a Balinese wishes emphatically to protest his innocence: "*Apang gondong tiang toesing nawang*", which means "May I get goitre if I know anything about it".

Celebes and Timor

Goitre occurs at Madjene and at Maros on the west coast of Celebes (Donath [1150] and Noosten [1159]) Two other centres are marked on Noosten's map of this oddly shaped island, one almost at the tip of the northern arm in the neighbourhood of Kotamobagoe and the other near Masamba in *central* Celebes due north of the Gulf of Bone.

expressionless faces, noses with widely patent nostrils and depressed bridges thick lips, exaggerated bossing of the skull, and various degrees of mental retardation. Many of the good-natured dwarfs show a specious giggling brightness; not a few are deaf or dumb, or both. The worst cases, sub-human in appearance, are seldom seen, as they are hidden in the jungle at the approach of strangers.

Some half-hearted attempts have been made to supply the natives with iodized salt in certain areas of the interior by means of air-drops or by overland routes In Heim's experience (personal communication, 1953) the natives would readily take to iodized salt and in some instances have themselves requested the Government to arrange for its purchase.

Sarawak

T. Harrisson (personal communication to I. Polunin,[1146] 1951) who has made a special study of goitre in Sarawak, states that the disease is common in certain inland areas, sometimes to a serious extent, whereas other inland areas not far distant are completely non-goitrous. This immunity applies particularly to the Kelabit country, which covers the upper Baram river district in the interior of the 4th and 5th Divisions of Sarawak. Here the people are goitre-free because they use an iodine-rich salt derived from local salt springs, of which there are about twenty or thirty in the neighbourhood By contrast, in the areas of the interior where goitre occurs Kelabit salt is unobtainable and people rely solely on imported salt

Samples of Kelabit salt have been chemically examined by B. W. Simpson (personal communication to I. Polunin,[1146] 1951), who found an iodine content of 10.5 mg per kg (i e , 1 in 95 240), and later by M. M. Murray (personal communication, 1955) who found 65 2 mg per kg (i e., 1 in 15 330). Even the lower of these levels would be quite sufficient to prevent goitre in a community regularly using this salt.

W G Evans (personal communication, 1955) writes that some of these protective salt springs in the Kelabit country are no more than a wet seepage out of the ground; the local people, having first prepared the ground, insert a hollow tree-trunk deep into the origins of the water to make what is in effect a narrow well The saline water is then siphoned out and subjected to a lengthy evaporation process by vigorous boiling over a wood fire. The salt thus produced is a very valuable commodity in the Kelabit outland and although it is not possible to place a monetary value on it because cash is so little used in these parts, it can be said that a few ounces are sufficient payment for a hard day's work.

The natives fully appreciate that their freedom from goitre is due to their use of this salt, and for this reason Kelabit salt is not only esteemed for its protective virtues but also has a reputation as a curative for existing goitre.

added iodine It was proved that if the loose salt were stored dry in bamboo containers near the fire according to local custom, no loss of iodine occurred.

North Borneo

Goitre is endemic over a large area of North Borneo; it is regarded with much aversion by all natives and is responsible for a great deal of the inbreeding and degeneration which has occurred there (Clarke;[1172] Mazat;[1174] Regester.[1175] F Heim—personal communication, 1953) In the country of the Muruts and Dusuns, primitive aboriginal peoples living in the southern part of the Colony roughly south of a line joining the northern shores of Brunei Bay on the west coast with Mount Trusmadi in the interior, the principal endemic areas are the Bokan country, Ulu Kinabatangan, Tomani area, Bole district and Ulu Mengalong

The best modern account of goitre in these communities is by Regester[1175] who emphasizes the ubiquity of the disease, wherever he went, the great majority of people had clearly visible fullness of the thyroid Exophthalmic goitre, toxic or degenerative changes, myxoedema and cretinism he never saw

On a two-week medical mission into the Murut jungle in 1958, Mazat[1174] encountered a 90% occurrence of colloid goitres "of huge dimensions". In contrast to Regester, he saw typical signs of cretinism akin to those recorded by Clarke[1172]

The disease also occurs sporadically in the hills to the west of the Keningau plain, in the Dalit, and between Melalap, Tenom and Kamabong. Other goitre centres that have been named are the Pansia district of Sipitang; Bundu Tuhan in Ranau, the Tambunan hills, especially Monsak village; the Lanas district of Tulid, and the hill regions of Kudat.

Systematic clinical surveys have not been made, but reports from medical officers fix the goitre rate at anything between 1% and 25%. F Heim (personal communication, 1953) describes the prevalence at three Minokok villages in Upper Kinabatangan as "rather high", and a rate of 33.6% has been recorded among 1014 natives examined in the Bokan country[1173] The disease is between two and three times as frequent in females as in males Usually the thyroid swelling becomes apparent about puberty and may reach a very large size in adult life. Thyrotoxicosis is rare

The goitre centres are mostly situated in jungle-clad hilly country of sand and limestone through which the streams and rivers run rapidly over stones and boulders. Clarke[1172] found it an unusually interesting experience to conduct clinics in areas where cretinism is endemic The hill Kwijaus and the Muruts living in the secluded goitre-bearing hills of the middle Padas between Kamabong and Bole are particularly affected. Briefly, outstanding features are reduction in height, often with disproportionate shortening of the limbs, a general physical podginess with thick dry skin, short thick fingers, protuberant abdomen, perhaps umbilical hernia, dull

of Peking, drinking-water is hard, but only occasional thyroid enlargement was seen; in the mountainous region farther north, however, the water is obtained largely from shallow surface wells and is undoubtedly soft. It is almost always boiled before use. Here, by a rough and ready method, Bolt estimated the goitre rate to be 40% in men and 60% in women. When questioned about their neck growths the people affirmed that they were due to a *lack* of something in the water and even claimed that they arose because the water was soft. This recalls conditions in Malaya (see page 167) and suggests an absolute deficiency of iodine as the cause, and not pollution or the presence in water of any other goitrogenic factor. Bolt also noticed the peculiar fact, which may or may not be relevant, that the shells of hens eggs in this vicinity are much thinner than usual and that many of them are so deficient in lime salts as to leave the egg membranous in places.

Writing of this area, Adolph & Ch'en [1176] mention especially the intensity of the disease near the Western Tombs and Eastern Tombs (Imperial Burial Grounds) situated respectively to the south-west and north-east of Peking in the Province of Hopeh Entire villages in these regions are reported to be almost 100% goitrous Analyses by Adolph & Ch'en show that the iodine content of water and foodstuffs from the environs of these mausolea is generally speaking less than that of foods and water collected in non-goitrous parts of Hopeh and the neighbouring Provinces of Shantung and Shansi Adolph & Whang [1178] also found adequate amounts of iodine in vegetable foods from the Soochow-Shanghai area, where simple goitre is extremely rare or non-existent.

The goitres of North China—and this is particularly true of the Peking district—are of the non-toxic type; the swellings vary in size from that of a hen's egg to that of a melon (Bolt [1179])

Western China

During his several expeditions through the Provinces of Kansu, Szechwan, Kweichow and Yunnan in western China, Hosie [1186, 1187] saw goitre at many places, in both sexes, and at all ages. King [1190] confirms that parts of Kansu, particularly the high plateau south of the Mongolian border watered by the upper reaches of the Yellow River (Hwang Ho), are very goitrous Spring water or the water of mountain streams in which the roots of willows or other trees are exposed is the native explanation of the cause The disease is also prevalent in the Gold River district on the China-Tibetan border where a survey has been carried out by Liljestrand.[1195] It is frequent, too, in the Sungpan region to the north-west of Szechwan. Here, the people eat Ching salt and Tsou salt, both of which contain barely sufficient iodine (1: 111 000 and 1: 170 000, respectively) to protect against the action of any strong local goitrogenic agent. It is believed by Cheng & Ku [1180] that the customary high cabbage dietary of the Sungpan people is responsible for tipping the scales to the side of iodine insufficiency.

China (mainland)

Endemic goitre is of ancient lineage in China. From time immemorial travellers penetrating into the fastnesses of its northern, western and south-western provinces have been struck by the evidences of human misery and degradation due to goitre and cretinism; their diaries and journals are full of vivid impressions which these scenes have made

The Chinese term for goitre is *Ying*, meaning a tassel hanging from the neck. Lee [1193] cites references showing that the disease was known in China in the third century B.C. and that its treatment by alcoholic infusion of seaweed was practised at that time Marco Polo [348] saw goitres in the Chinese Turkestan provinces of Kashgar and Yarkand when on his famous travels from Venice to the court of the Grand Khan about the year 1275. Six centuries later, Hosie [1186, 1187] speaks of the " enormous and unsightly " goitres he encountered when journeying through the Provinces of Szechwan, Kweichow and Yunnan in western China; and Warwick [1213] makes similar references to the prevalence of the malady in many sections of the Great Wall, along which he explored for a thousand miles in the early 1920's

Other Western writers who recount like experiences in different parts of China are Hewett,[1185] Lewis,[1194] Bolt,[1179] King,[1190] Rock,[1207] Miller,[1199-1201] Maxwell,[1198] McClendon,[1197] and Robertson.[1204-1206] In recent years Oriental medical scientists have themselves added greatly to the documentation [a]

The main goitre belt begins in the north-east of the country in the neighbourhood of Shanhaikwan on the southern border of Manchuria (now the North-East Administrative Area of China); it follows a westward semicircular route across the mountainous watershed north of Peking into Chahar and Suiyuan, and then turns south through the Province of Kansu as far as Chinghai From thence it extends through Sikang and the western regions of Szechwan and Kweichow into Yunnan, the most goitrous province in all China With the possible exception of Tsungming Island in the mouth of the Yangtse where goitre has been noted by Maxwell,[1198] all the coastal provinces, including those of the great plain in the east-centre of the country, are virtually goitre-free, at least so far as the simple endemic variety is concerned; but everywhere in these provinces cases of Graves' disease are frequent. Indeed, of all goitre cases brought to Miller's [1201] attention in these areas about 60% were toxic. A good goitre map of China is given by Liu & Chu.[1196]

Northern China

On a journey from Peking northward to Jehol via the plain of Chihli, Tungchow, Yenchiao, San-Hohsien and Chichou, Bolt [1179] found well-marked endemic goitre nests in the mountainous country extending up into the Feng Shui Ti district. Throughout the fertile plain of Chihli to the east

---

[a] See references 1177, 1180, 1188, 1189, 1191-1193, 1196, 1202, 1203 and 1209-1213 in the bibliography

of Peking, drinking-water is hard, but only occasional thyroid enlargement was seen; in the mountainous region farther north, however, the water is obtained largely from shallow surface wells and is undoubtedly soft. It is almost always boiled before use Here, by a rough and ready method, Bolt estimated the goitre rate to be 40% in men and 60% in women. When questioned about their neck growths the people affirmed that they were due to a *lack* of something in the water and even claimed that they arose because the water was soft This recalls conditions in Malaya (see page 167) and suggests an absolute deficiency of iodine as the cause, and not pollution or the presence in water of any other goitrogenic factor. Bolt also noticed the peculiar fact, which may or may not be relevant, that the shells of hens eggs in this vicinity are much thinner than usual and that many of them are so deficient in lime salts as to leave the egg membranous in places

Writing of this area, Adolph & Ch'en [1176] mention especially the intensity of the disease near the Western Tombs and Eastern Tombs (Imperial Burial Grounds) situated respectively to the south-west and north-east of Peking in the Province of Hopeh Entire villages in these regions are reported to be almost 100% goitrous. Analyses by Adolph & Ch'en show that the iodine content of water and foodstuffs from the environs of these mausolea is generally speaking less than that of foods and water collected in non-goitrous parts of Hopeh and the neighbouring Provinces of Shantung and Shansi Adolph & Whang [1178] also found adequate amounts of iodine in vegetable foods from the Soochow-Shanghai area, where simple goitre is extremely rare or non-existent

The goitres of North China—and this is particularly true of the Peking district—are of the non-toxic type; the swellings vary in size from that of a hen's egg to that of a melon (Bolt [1179])

Western China

During his several expeditions through the Provinces of Kansu, Szechwan, Kweichow and Yunnan in western China, Hosie [1186, 1187] saw goitre at many places, in both sexes, and at all ages King [1190] confirms that parts of Kansu, particularly the high plateau south of the Mongolian border watered by the upper reaches of the Yellow River (Hwang Ho), are very goitrous Spring water or the water of mountain streams in which the roots of willows or other trees are exposed is the native explanation of the cause The disease is also prevalent in the Gold River district on the China-Tibetan border where a survey has been carried out by Liljestrand [1195] It is frequent, too, in the Sungpan region to the north-west of Szechwan. Here, the people eat Ching salt and Tsou salt, both of which contain barely sufficient iodine (1 111 000 and 1: 170 000, respectively) to protect against the action of any strong local goitrogenic agent It is believed by Cheng & Ku [1180] that the customary high cabbage dietary of the Sungpan people is responsible for tipping the scales to the side of iodine insufficiency.

China (mainland)

Endemic goitre is of ancient lineage in China From time immemorial travellers penetrating into the fastnesses of its northern, western and south-western provinces have been struck by the evidences of human misery and degradation due to goitre and cretinism; their diaries and journals are full of vivid impressions which these scenes have made

The Chinese term for goitre is *Ying*, meaning a tassel hanging from the neck. Lee [1193] cites references showing that the disease was known in China in the third century B.C. and that its treatment by alcoholic infusion of seaweed was practised at that time. Marco Polo [393] saw goitres in the Chinese Turkestan provinces of Kashgar and Yarkand when on his famous travels from Venice to the court of the Grand Khan about the year 1275. Six centuries later, Hosie [1186, 1187] speaks of the "enormous and unsightly" goitres he encountered when journeying through the Provinces of Szechwan, Kweichow and Yunnan in western China, and Warwick [1215] makes similar references to the prevalence of the malady in many sections of the Great Wall, along which he explored for a thousand miles in the early 1920's.

Other Western writers who recount like experiences in different parts of China are Hewett,[1185] Lewis,[1194] Bolt,[1179] King,[1190] Rock,[1207] Miller,[1199-1201] Maxwell,[1198] McClendon,[1197] and Robertson [1204 1206] In recent years Oriental medical scientists have themselves added greatly to the documentation.[a]

The main goitre belt begins in the north-east of the country in the neighbourhood of Shanhaikwan on the southern border of Manchuria (now the North-East Administrative Area of China), it follows a westward semicircular route across the mountainous watershed north of Peking into Chahar and Suiyuan, and then turns south through the Province of Kansu as far as Chinghai From thence it extends through Sikang and the western regions of Szechwan and Kweichow into Yunnan, the most goitrous province in all China With the possible exception of Tsungming Island in the mouth of the Yangtse where goitre has been noted by Maxwell,[1198] all the coastal provinces, including those of the great plain in the east-centre of the country, are virtually goitre-free, at least so far as the simple endemic variety is concerned; but everywhere in these provinces cases of Graves' disease are frequent. Indeed, of all goitre cases brought to Miller's [1201] attention in these areas about 60% were toxic A good goitre map of China is given by Liu & Chu [1196]

Northern China

On a journey from Peking northward to Jehol via the plain of Chihli, Tungchow, Yenchiao, San-Hohsien and Chichou, Bolt [1179] found well-marked endemic goitre nests in the mountainous country extending up into the Feng Shui Ti district Throughout the fertile plain of Chihli to the east

[a] See references 1177, 1180, 1188, 1189, 1191-1193, 1196, 1202, 1203 and 1208-1213 in the bibliography

among the mountain Kaws inhabiting the Ksiulungkiang (Chili) region of southern Yunnan.

From his exhaustive studies, Robertson [1204-1206] concluded that extreme environmental iodine deficiency aggravated by an excessively hard water-supply is the cause of goitre in Yunnan. Proof of this is seen in the fact that the disease is not usually so severe, if it exists at all, among communities in West China who are accustomed to using local salts rich in iodine—for example, the salt mined at Nanlang in Szechwan. The salt derived from Yunnan mines is deficient in iodine and Robertson suggested that as a partial preventive measure it should be mixed with Szechwan salt in equal parts.

To arrange systematic goitre surveys in Yunnan and to organize preventive measures, an advisory committee entitled the Yunnan Anti-Goitre Association has been formed under the honorary presidency of the Governor of the Province.

Southern China

Jeanselme [1142] refers to Simon's observation of goitre among mountain-dwellers in the environs of Lungchow, a town in the Province of Kwangsi close to the North Viet Nam border. Farther to the east, Lewis [1191] unexpectedly came upon a strong focus of goitre in the Province of Hunan when journeying over the mountains between Lanshan and Lienchow. Nearly at the top of the ridge is a village where he saw greatly enlarged thyroids in large numbers. The villagers told him that the disease was of long standing and that practically the entire adult population were victims.

North-East China (formerly Manchuria)

Yamaguchi of the Manchuria Medical College, Mukden, was the first to take up the scientific study of goitre in former Manchuria. He published his results in the *Journal of the South Manchuria Medical Society* in 1921, but in spite of much effort the present writers have not been able to see Yamaguchi's original accounts and it is believed that many who quote him can never have seen them either. Apparently the reports cover the incidence of the disease according to locality, sex and age, and call attention to the possibly decisive role that an excess of lime in drinking-water may play in causation. Yamaguchi's work was continued by his colleagues, and between 1935 and 1939 detailed studies of the Manchurian endemic and its relation to environmental iodine supply were published by Kodama, Suzuki & Masayama,[1181] Takei and his colleagues,[1211-1213] Takamori,[1209, 1210] Noda,[1202] and others. No recent accounts of goitre in former Manchuria appear to exist.

The principal focus lies in Jehol, the province in the south-west of North-East China (formerly Manchuria) adjoining Hopeh in North China. Here, the endemic may be regarded as continuous with that already described

But, of all goitrous Chinese provinces, the one about which most has been written is Yunnan on the borders of Burma in the south-west. Writing of Kakatang, a village on the Weisi—a tributary of the Mekong river—in northern Yunnan west of Likiang, Rock [1207] says. "What sights one can behold in such a place as Kakatang! *Nowhere have I seen goiter so prevalent* as here. The people carried regular pouches in their throats like certain monkeys when they fill up with peanuts One man, half blind, was loaded down with a goiter so huge that the weight of it dragged down his lower jaw, making it difficult for him to keep his mouth closed."

The most impressive accounts of goitre in Yunnan are those by Jeanselme [1142] and by Robertson [1205 1206] The former entered Yunnan from the south after completing his goitre survey of Indo-China and saw many cases in the villages and market-places frequented by the mountain-dwellers between Man Hao on the southern border and Kunming (Yunnanfu), the capital of the province Jeanselme estimated the over-all rate in Kunming to be 20%, and he records that the disease is no less severe in the prefecture of Kai Hoa, lying farther to the east. At Tali, and all around the great lake on which Tali is situated, Jeanselme saw many myxoedematous cretins with wan and puffy faces and unsteady gait

Conditions as revealed by Robertson's survey some thirty years later were no different He was concerned chiefly with the health status of peoples living along the route of the great Burma-China highway and in the adjoining country Inspection of the adult population of both sexes working in labour gangs during the construction of the road disclosed a goitre rate of 80% in some gangs, the average in all gangs being over 50%

Robertson was much struck with the patchy distribution of the Yunnan endemic. In the north west, the people all along the valleys of the Salween, Mekong and upper Yangtse rivers are very heavily affected, but the disease is not so evident west of Pao-shan Similarly, on the road from Kunming to Hwei-tsheh in the north-east there are villages in which almost everybody has a goitre, whereas Hwei-tsheh itself is not markedly goitrous Robertson explains the patchy distribution on geological grounds. In the western part of the province, before one comes to the canyons of the Mekong and Salween, the country is composed of irregular ranges of upper grasslands and undulating plains where pastoral agriculture is intensively practised. Much of this country is on porous limestone soil and it is here, in remote villages, that goitre is evident both in man and in his flocks and herds Throughout the lower-lying parts of the province where rice, potatoes, wheat, and fruits and vegetables of all sorts are cultivated, the disease is not so prominent.

Others who have commented on goitre occurrences in this general area are A. J. Broomhall (personal communication, 1950), who speaks of the frightful goitres seen in the Si-Chang district of Sikang, and Galt,[1181] who describes the disease as fairly common among the Tai and almost universal

The highest rates are in areas underlain by pre-Cambrian and limestone formations.

There are no recent reports regarding preventive measures in former Manchuria, but twenty years ago treatment by means of iodine was carried out in parts of Lingyuan, one of the worst districts of Jehol, and marked improvement was noticed after about two months Of 9 children treated under 10 years of age, 6 recovered; of 56 between 10 and 20 years, 12 recovered.

Recent preventive drive

Establishment of the People's Republic of China in 1949 brought organized improvement into every branch of public health, including co-ordinated efforts to assess the extent of goitre and stamp it out. Since 1958 the application of prophylactic and therapeutic measures has leapt ahead in practically all endemic areas

The campaign has involved examination of 7 585 311 persons of whom 592 702 were found to have goitre. This means an average rate of 7.8%, but, as seen in Table XXI, rates vary locality by locality from 2.8% in Kirin Province (North-East China, formerly Manchuria) to 82.3% in the mountainous far western Province of Kansu

The chief prophylactic method adopted is the supply of iodized salt; but traditional drugs containing iodine, iodized oil, and potassium iodide in fairly large doses are also employed One year after the introduction of

TABLE XXI PREVALENCE OF GOITRE IN CHINA

Province	Locality (no of areas surveyed)	Individuals examined	Number with goitre	Percentage with goitre	Percentage range
Kirin	Li Shu	454 117	12 837	2.8	
Hopeh	Changchiakou (3)	8 536	1 249	14.6	
"	Ching Lung (3)	2 308	1 632	70.7	
"	Yi	326 811	49 021	15.0	
Shansi	Tai Ku & Hsin Yuan	4 135	2 244	51.8	34-61
"	Chieh Hsiu (5)	2 962	705	23.8	
Honan	Lu Shan	422 181	130 581	24.5	
"	Nanyang	6 352 418	391 334	6.1	1-30
Hupeh	Huang Chan	9 950	1 540	15.5	9-34
Hunan	Chien Yang	—	438 685	—	1-70
Kansu	Hsu Kou & Kao Chia	1 893	1 559	82.3	
		7 585 311	592 702 *	7.8	

* Total excludes Hunan, number examined is not available

as occurring along the Great Wall north of Peking. It particularly affects the district of Pingchuan and the north side of the Wall, but is also severe farther to the north and north-west at Lingyuan, Chengteh, Luanping, Lunghwa, Chihfeng and Weichang.

The goitre prevalent in Jehol is classified by Takei [1212] and Takamori [1209] as belonging to the Alpine type and is commonly associated with deaf-mutism, idiocy, cretinism and myxoedema. The goitre rate varies between 10% and 60% and may be as high as 85% in the Pingchuan area. Chinese and Mongolians are equally prone to the disease and immigrant Japanese rapidly become victims; a Japanese non-commissioned officer acquired a goitre four months after entering the country and a consular police official contracted a second-degree thyroid enlargement (Dieterle's scale) within nine months of being stationed at Pingchuan. As usual, incidence is higher in females than in males; infants are occasionally affected.

East of Jehol, goitre occurs in the basin of the river Liao and in the upland parts of the Liaotung peninsula, where Siuyen (west of Antung) and Huanjen are especially mentioned. Elsewhere in former Manchuria there are goitre pockets to be found throughout the eastern hills, for example at Tunghwa and Mishan which lie 300 and 600 miles north-east of Antung and Mukden, respectively. Other centres are found at Hulan and Suihwa immediately north of Pingkiang (Harbin), and throughout the Khingan Mountains in the extreme north at the head-waters of the Nonni river (McClendon; [1197] Noda [1202])

The results of various analytical and biochemical investigations have been advanced by the Mukden medical school and their associates as evidence that the principal cause of goitre in former Manchuria is insufficiency of iodine in soils,[1202] water [1191, 1208] and local foods [1212] By themselves, the data are not wholly convincing unless other factors are taken into account. For example, well-waters from Jehol, where goitre is rife, register from 4 μg to 14 μg of iodine per litre, a level at which goitre would not normally be expected to arise. It must be remembered, however, that waters in the Jehol area are so excessively hard that an iodine level of even 14 μg per litre may fail to protect. At Talien (Dairen), on the goitre-free tip of the Liaotung peninsula, the water contains 24 μg of iodine per litre.

Studies by Noda [1202] not only in Jehol but throughout the whole of former Manchuria show that the amount of iodine in soils where goitre prevails is distinctly less than that in soils from non-goitrous districts, thus

Prevalence of goitre	*Soil iodine (μg per kg)*
Nil (peninsular Liaotung)	2 249
Nil (Upper Sungari)	1 567
Under 10%	1 397
10% to 50%	1 053
Over 50%	791

made by Kawaishi,[1227] Hashimoto & Kyo,[1225] Hashimoto & Sha,[1226] Kawaishi & Hashimoto,[1254] Chen,[1220-1224] and Ko.[1228-1233] Some representative results are shown in Table XXII

TABLE XXII PREVALENCE OF GOITRE IN TAIWAN

Area	Number of people examined	Number of people with goitre	Percentage with goitre	Bibliographical reference no
Entire Island (over-all prevalence)	318 116	26 979	8.5	1227
Ōka district of Taihoku	23 463	6 200	26 4	1225
Pinan and Dainan districts of Taitō	4 060	745	18.3	1226

The rate in the north and west was highest at Sekitokei in the Oka area (45 4%) and lowest at Taiko (17 2%) Cases were especially numerous in the region of the Kanwen delta (40 7%) and in the basin of the Tansui river Rates in the Pinan and Dainan regions of Taitung varied from 5% at Miwa to 26 7% at Rika The highest rate (63 5%) was recorded by Kawaishi & Hashimoto [1254] in the Shirakawa of Mizuho in the foothills on the mid-eastern side of the country Topographical features of the endemic region have been thoroughly investigated by Ko [1225 1231]

Evidence points strongly to the fact that insufficient iodine intake is the main cause of goitre in Taiwan Ko [1230] incriminates the sandy and alluvial soils characteristic of practically every goitre area in the country, and believes that nutritionally-deficient vegetable foods grown on these soils are largely accountable Kawaishi [1227] considers, however, that mere iodine deficiency is not entirely responsible and that geochemical and climatic factors which raise the demand for iodine must also be taken into account. Since hypercalcaemia is rather common among goitrous people in Taiwan, a deranged calcium metabolism is regarded by Kawaishi as possibly associated with goitre causation Sai [1235] examined this question but could find no statistically significant relationship between the blood-calcium level and the type and extent of thyroid enlargement in cases of endemic goitre in Taiwan There was, however, a tendency for the urinary excretion of calcium and potassium to be greater than normal in both endemic goitre and Basedow's disease

On returning to his native village—Chiushe in central Taiwan—after an absence of some years during the 1939-1945 war, Chen [1221, 1224] was struck by the noticeable increase in simple goitre Formerly, goitre had not been prevalent to any marked degree in this district and its emergence suggested the existence of some goitrogenic influence engendered by wartime condi-

iodized salt (1 5000) into Changchiakou, re-examination of the populace disclosed no new goitre cases in that area In Hunan, re-examination of 264 goitrous individuals two months after the introduction of iodized salt (1 100 000 or 1: 50 000) revealed a reduction in the circumference of the neck in 63% of these cases Similar satisfactory results with iodized salt, *iodine-containing drugs and iodized oil have been obtained elsewhere in* China [1182, 1183]

Animal goitre in China

Imperfect calcification of hens' eggs—a common occurrence in the mountain country north of Peking—has already been mentioned as possible evidence of iodine deficiency. From the same area comes Geil's observation (see Warwick [1215]) that goitrous antelope are not unusual in the Imperial Forest Preserve at the Tung Ling or Eastern Tombs. Robertson [1205, 1206] suggests that iodine deficiency is the cause of abortion in cows in Yunnan Province, and preliminary observations led him to believe that many horses and cattle in West China suffer from lack of both salt and iodine.

Korea

Apparently the only part of Korea where goitre is endemic is the Kangai neighbourhood in the northern hilly section of the country Here, according to Mills,[1216, 1217] simple goitre is quite common in various stages of development, *and the Koreans have a saying that anyone who drinks the water* that drains from the decaying roots of the edible pine will develop the disease.

Smith [1218] suggests that in all probability the fact that no part of the Korean peninsula is far removed from the sea, and that sea foods are a large factor in the diet of the people, accounts for the comparative rarity of endemic goitre in the country *On the other hand, at the time of writing* (1928), he could discern that cases of hyperthyroidism were on the increase throughout Korea

A survey of the nutritional status of Korean military forces conducted by Williams et al [1219] in 1956 disclosed virtually no evidence of goitre. Palpable thyroid enlargement was observed in only 0.8% of individuals examined.

Taiwan

Goitre is exceedingly common in Taiwan Maxwell [1198] records that in certain mountain villages almost all the inhabitants have the disease Affected areas include the Ōka area of Taipeh (Taihoku) District in the north, the Taiko neighbourhood in the west, the Chiushe-Houli-Fengyuan area in the centre, and the regions of Pinan and Dainan in Taitung (Taitō) District in the south-east of the island Surveys of prevalence have been

made by Kawaishi,[1227] Hashimoto & Kyo,[1225] Hashimoto & Sha,[1226] Kawaishi & Hashimoto,[1224] Chen,[1220-1221] and Ko.[1228-1233] Some representative results are shown in Table XXII.

TABLE XXII. PREVALENCE OF GOITRE IN TAIWAN

Area	Number of people examined	Number of people with goitre	Percentage with goitre	Bibliographical reference no.
Entire island (over-all prevalence)	318 116	25 979	8.5	1227
Ōka district of Taihoku	23 453	6 200	26.4	1225
Pinan and Dainan districts of Taitō	4 060	745	18.3	1226

The rate in the north and west was highest at Sekitokei in the Ōka area (45.4%) and lowest at Taiko (17.2%). Cases were especially numerous in the region of the Kanwen delta (40.7%) and in the basin of the Tansui river. Rates in the Pinan and Dainan regions of Taitung varied from 5% at Miwa to 26.7% at Rika. The highest rate (63.5%) was recorded by Kawaishi & Hashimoto[1224] in the Shirakawa of Mizuho in the foothills on the mid-eastern side of the country. Topographical features of the endemic region have been thoroughly investigated by Ko.[1228-1231]

Evidence points strongly to the fact that insufficient iodine intake is the main cause of goitre in Taiwan. Ko[1230] incriminates the sandy and alluvial soils characteristic of practically every goitre area in the country, and believes that nutritionally-deficient vegetable foods grown on these soils are largely accountable. Kawaishi[1227] considers, however, that mere iodine deficiency is not entirely responsible and that geochemical and climatic factors which raise the demand for iodine must also be taken into account. Since hypercalcaemia is rather common among goitrous people in Taiwan, a deranged calcium metabolism is regarded by Kawaishi as possibly associated with goitre causation. Sai[1235] examined this question but could find no statistically significant relationship between the blood-calcium level and the type and extent of thyroid enlargement in cases of endemic goitre in Taiwan. There was, however, a tendency for the urinary excretion of calcium and potassium to be greater than normal in both endemic goitre and Basedow's disease.

On returning to his native village—Chiushe in central Taiwan—after an absence of some years during the 1939-1945 war, Chen[1221, 1222] was struck by the noticeable increase in simple goitre. Formerly, goitre had not been prevalent to any marked degree in this district and its emergence suggested the existence of some goitrogenic influence engendered by wartime condi-

iodized salt (1 5000) into Changchiakou, re-examination of the populace disclosed no new goitre cases in that area. In Hunan, re-examination of 264 goitrous individuals two months after the introduction of iodized salt (1 100 000 or 1: 50 000) revealed a reduction in the circumference of the neck in 63% of these cases Similar satisfactory results with iodized salt, iodine-containing drugs and iodized oil have been obtained elsewhere in China [1182, 1183]

Animal goitre in China

Imperfect calcification of hens' eggs—a common occurrence in the mountain country north of Peking—has already been mentioned as possible evidence of iodine deficiency From the same area comes Geil's observation (see Warwick [1215]) that goitrous antelope are not unusual in the Imperial Forest Preserve at the Tung Ling or Eastern Tombs. Robertson [1205, 1206] suggests that iodine deficiency is the cause of abortion in cows in Yunnan Province, and preliminary observations led him to believe that many horses and cattle in West China suffer from lack of both salt and iodine.

Korea

Apparently the only part of Korea where goitre is endemic is the Kangai neighbourhood in the northern hilly section of the country. Here, according to Mills,[1216, 1217] simple goitre is quite common in various stages of development, and the Koreans have a saying that anyone who drinks the water that drains from the decaying roots of the edible pine will develop the disease

Smith [1218] suggests that in all probability the fact that no part of the Korean peninsula is far removed from the sea, and that sea foods are a large factor in the diet of the people, accounts for the comparative rarity of endemic goitre in the country On the other hand, at the time of writing (1928), he could discern that cases of hyperthyroidism were on the increase throughout Korea

A survey of the nutritional status of Korean military forces conducted by Williams et al [1219] in 1956 disclosed virtually no evidence of goitre Palpable thyroid enlargement was observed in only 0 8% of individuals examined.

Taiwan

Goitre is exceedingly common in Taiwan Maxwell [1198] records that in certain mountain villages almost all the inhabitants have the disease Affected areas include the Ōka area of Taipeh (Taihoku) District in the north, the Taiko neighbourhood in the west, the Chiushe-Houli-Fengyuan area in the centre, and the regions of Pinan and Dainan in Taitung (Taitō) District in the south-east of the island Surveys of prevalence have been

made by Kawaishi,[1227] Hashimoto & Kyo,[1225] Hashimoto & Sha,[1226] Kawaishi & Hashimoto,[1234] Chen,[1220-1221] and Ko.[1228-1233] Some representative results are shown in Table XXII

TABLE XXII PREVALENCE OF GOITRE IN TAIWAN

Area	Number of people examined	Number of people with goitre	Percentage with goitre	Bibliographical reference no
Entire Island (over-all prevalence)	318 116	26 979	8 5	1227
Ōka district of Taihoku	23 463	6 200	26 4	1225
Pinan and Dainan districts of Taitō	4 060	745	18 3	1226

The rate in the north and west was highest at Sekitokei in the Ōka area (45 4%) and lowest at Taiko (17.2%) Cases were especially numerous in the region of the Kanwen delta (40 7%) and in the basin of the Tansui river Rates in the Pinan and Dainan regions of Taitung varied from 5% at Miwa to 26 7% at Rika. The highest rate (63 5%) was recorded by Kawaishi & Hashimoto [1254] in the Shirakawa of Mizuho in the foothills on the mid-eastern side of the country Topographical features of the endemic region have been thoroughly investigated by Ko [1228 1231]

Evidence points strongly to the fact that insufficient iodine intake is the main cause of goitre in Taiwan Ko [1230] incriminates the sandy and alluvial soils characteristic of practically every goitre area in the country, and believes that nutritionally-deficient vegetable foods grown on these soils are largely accountable. Kawaishi [1227] considers, however, that mere iodine deficiency is not entirely responsible and that geochemical and climatic factors which raise the demand for iodine must also be taken into account. Since hypercalcaemia is rather common among goitrous people in Taiwan, a deranged calcium metabolism is regarded by Kawaishi as possibly associated with goitre causation Sai [1235] examined this question but could find no statistically significant relationship between the blood-calcium level and the type and extent of thyroid enlargement in cases of endemic goitre in Taiwan There was, however, a tendency for the urinary excretion of calcium and potassium to be greater than normal in both endemic goitre and Basedow's disease

On returning to his native village—Chiushe in central Taiwan—after an absence of some years during the 1939-1945 war, Chen [1221, 1224] was struck by the noticeable increase in simple goitre Formerly, goitre had not been prevalent to any marked degree in this district and its emergence suggested the existence of some goitrogenic influence engendered by wartime condi-

tions Indeed this is probably true, the local dietary had perforce changed from one of rice, potatoes, green vegetables, pork, beef, sea-food, lard and peanut oil, to a less vital diet consisting of cabbage, potatoes, bean leaves, cassava, wheat, and the seed-oils of rape and flax. Little wonder that physical disabilities obtruded—with evident thyroid enlargement among the first symptoms.

Over nine years and eight months, May 1945 to December 1954, Chen [1223] administered therapeutic doses of iodine (average dose 1 5 mg daily) to 2838 goitre patients in the Chiushe area A favourable response was observed in 63 3% of cases.

In regions where human goitre is endemic, thyroid enlargement also occurs among pigs Kobayashi [1234] examined the thyroids of 200 castrated male and female pigs and found no less than 81% of enlarged thyroids in those from Ōka village One gland weighed 550 g In Hwalien (Karenkō) District, where there is a 65%-70% rate of human goitre, 48% of pigs were affected. Histological sections taken from thyroids which outwardly appear normal reveal cellular changes indicating that so-called " normal " glands from this area are already in a pre-goitrous state before visible enlargement begins Castration has no influence on the development of goitre in pigs.

Japan

There is general agreement that, compared with other countries in the same geographical region, simple goitre is not a problem of any magnitude in the main islands which make up Japan—Honshu, Hokkaido, Kyushu, and Shikoku On one occasion, McClendon went looking for goitres in likely places in the interior but could find no more than four cases among 20 000 inhabitants (McClendon,[1258-1262] Aschoff,[1239] Papellier,[1275] Kawaishi & Hashimoto [1254])

Comparative absence of the disease is ascribed by some to the widespread and regular habit of eating seaweed In Japan seaweed is served in a variety of ways as a constant article of diet and an amount of 10 g (dry), or even more, is often the portion for one person at a meal On average, 10 g of dry seaweed would contain about 5 mg of iodine

However, as Greenwald [1243] has pointed out, Japan is not by any means free from simple goitre. There are foci in mountainous inland localities, and on the coast, where thyroid enlargement is common; indeed, the rate may be quite high For example, in Gumma (Gunma) Prefecture in the interior of the country north of Tokyo, Hichijo [1246] found 11.1% of goitres among the 16 202 boys and girls he examined in 1953 Four years later, on a resurvey of Gumma children, he found 8% in boys and 14% in girls, and [illegible] nd 46% of girls were [illegible] rded by Hichijo [1246] [illegible] contrast with about 2% in the coastal town of Fujisawa south-west of Tokyo

Similarly, in Gifu Prefecture north of Nagoya in central Japan, Katsumata & Murakami [1253] examined 2434 girls and young women, of ages 13 to 26 years, at 15 different girls' schools and silk mills in 13 different localities, and found undoubted thyroid enlargement in 1242 (50%) of these subjects. Rates varied from 5.4% in a school at Seki situated on the plains at the edge of the mountains to 61% in a school at Funatsui, a town high in the Japanese Alps

It is true that the great majority of these enlargements (96%) were not visible to the naked eye and were only determinable on palpation. Nevertheless, the high prevalence of palpable thyroid enlargement among girls in the Gifu area indicates that the zone is potentially goitrous Katsumata & Murakami [1252] refer also to the occurrence of puberal goitre in Aichi Prefecture south-east of Nagoya and mention likewise that the Prefectures of Hyōgo and Okayama at the western end of Honshu are not immune The prevalence, however, is slight; a survey by Morinaga [1268] in 1950 showed only 4.6% of cases among 1480 children (6-14 years) at schools in the vicinity of Yakake in Okayama Prefecture, and 4.7% among 1516 outpatients attending Yakake hospital

At Kamikitayama in the Yoshino district of Nara Prefecture, the southernmost part of Honshu, Watanabe et al.[1292] saw goitres in 19.6% of children in their early school years But among children in middle school life the rate had jumped to 31.6% (26.6% in boys and 32.8% in girls) Other Prefectures in Honshu to which reference is made in the goitre literature of Japan are Tochigi,[1278] Chiba,[1219] Toyama [1269] and Tottori [1274]

Goitre foci are known also in Hokkaido, the most northerly island of the country Here, surveys have been made by Fujii, [1240, 1242] Hashiba, Ogawa & Otsuka; [1245] Inoue et al, [1251] Maeda et al, [1263] Morikawa et al; [1267] Okii; [1273] Takata, [1285, 1286] Takeda et al, [1287] and Usubuchi & Murotani [1291]

In the Hidaka highlands to the south of Hokkaido a rate of 3.05% has been recorded among a total of 4683 primary, junior and senior high-school minors of ages 6 to 18 years Incidence increases towards the east of the Hidaka region, reaching 7.3% to 12% at the coastal villages of Erimo, Meguro and Shoya situated at the tip of the Erimo peninsula Horoizumi, on the west coast somewhat north of Erimo, is another goitre centre In the south-west of the island Okii examined 2234 people in and around Esashi and found an over-all rate of 2.3%, the highest rate being in the area of Kamomejima Fujii [1240] describes goitre as endemic in a fishing village in Matsumae-gun at the extreme south-west of Hokkaido island. The offshore islands of Rebun, Rishiri, and Teuri to the far north-west of Hokkaido are also reputed to be goitrous (Usubuchi & Murotani; [1291] Inoue et al.[1251]).

Shikoku island contains a markedly endemic area in Ehime Prefecture to the west And on Kyushu, the only black spot appears to be Wakamatsu, a town right on the very northernmost extremity of the island—a situation exactly similar to that of Rebun and Rishiri (see above) and many others,

and full of provocative interest vis-à-vis the generally accepted theory of goitre genesis.

Field surveys and laboratory research on goitre among goats, dairy cows, beef-cattle, pigs and sheep in the endemic Nagano and non-endemic Toyama Prefectures of Honshu have been the immediate concern of Takamori and his colleague Yūki in a series of eight papers [1277-1281] Exceptionally heavy losses of newborn lambs and kids in Nagano during recent years are attributed to iodine deficiency for which the only preventive recommended by Takamori and his school is the iodization of animal-feeding salt in the proportion of one part of potassium (or sodium) iodide in every 1000 or 5000 parts of salt, depending on local circumstances In Hokkaido, the geographical coincidence of goitre in the animal population—horses particularly—and in the human population has been noted by Maeda et al [1263]

Philippines

According to Miller, the Filipinos show the highest goitre frequency of any people residing in the Orient The disease, he says, seems to be almost as prevalent in the Philippine Islands as in Switzerland [1300, 1301]

Early records collected by Greenwald [1296] prove that goitre was known in the Province of Batangas at the end of the eighteenth century, in the Province of Tayabas in 1845, and among the Bontoc Igorots in the highlands of northern Luzon at the beginning of the present century In 1905, Duncan [1293] reported its prevalence in a tribe living at Macabebe on the marshy northern shores of Manila Bay.

No systematic modern survey of prevalence has been made, but case-histories and hospital records relating to the number, type and provenance of thyroid patients operated upon in Philippine hospitals between 1909 and 1948 have been studied and analysed by various writers. These show that goitre is found in nearly all the 49 provinces composing the archipelago (Lopez-Rizal & Padua; [1299] Reyes, [1302] Erickson; [1294] Estrada, Nery & De Vera; [1295] Recio [1301])

The chief goitre region in the Philippines is the Province of Nueva Ecija in the central valley of Luzon where the twin municipalities of Peñaranda and Papaya are notorious as the home of goitre in the Islands Other centres in Luzon are: Bangued and Manabo in Abra Province in the north-west; the Bontoc district, the Province of Isabela on the east side, the area round Manila including Bulacan, Macabebe in Pampanga, and Cavite, the Bataan peninsula; and Tayabas and Batangas in the south of the island.

In the central islands of the archipelago there is goitre to be found on Panay at Capiz and Iloilo, and on Negros and Cebu Nichols [1300] noted the disease at Taytay, a town situated in the north of the island of Palawan; he remarks that as Taytay is on non-calcareous soil the goitre occurrence cannot be associated with excess of lime Actually, the geological formation

there consists of a water-laid volcanic tuff. In Mindanao, the southernmost part of the Philippines, goitre has been recorded at Lanao and in the valley of the river Sindangan

On the basis of a comparison between the relevant hospital returns for the 15 years up to 1924 and those for the two-and-a-half years following the liberation of the country at the end of the 1939-45 war, Recio [1301] concludes that thyroid disease has increased in the Philippines during recent years

Oceania

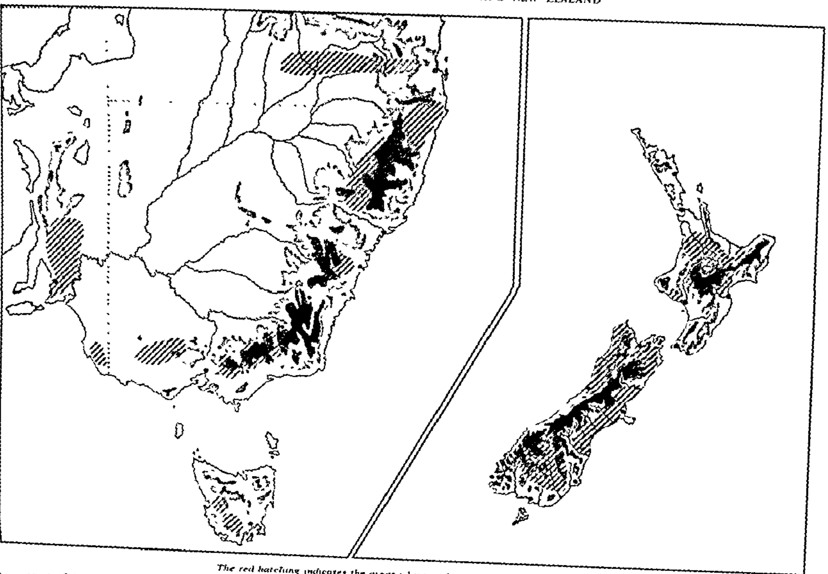
Soils are much richer in iodine than the rocks from which they are derived Eminent authorities who have critically examined the iodine cycle in nature believe that precipitation of iodine from the atmosphere is by far the most important agency through which soils are iodine-enriched. The explanation that iodine is mainly concentrated in soils as a residual component resulting from the weathering of underlying primary rocks is untenable, since such a process would call for the destruction and removal of incredible tonnages of other less-soluble rock or soil constituents

Atmospheric iodine originates from the sea, it is liberated from sea-water by oxidation and is carried inland by winds either in a gaseous state or adsorbed on floating particles of dust Air-borne iodine is brought down by rain or snow, the first rains of any rainy period contain more iodine than the later rains Addition of air-borne oceanic iodine to soil through rain or snow is a slow process, hundreds of thousands of years are required to build up an iodine-rich soil in this way

During the Ice Age the older iodine-rich soils were swept away and the whole course of soil evolution began afresh New soil-making materials were generated by the grinding-up of virgin crystalline rocks containing, at the most, one-tenth the average iodine content of mature agricultural soils As the ice cover receded, replenishment of the iodine in glacial and postglacial soil materials began—a process which is still in progress in some countries (see *Geochemistry of Iodine* [812])

As an introduction to goitre in Australia, New Zealand and the islands of Melanesia, this digression into the geochemistry of iodine is excused on two grounds First, Australia and New Zealand are among the countries in which the frequency distribution of goitre may be correlated with the areas and extent of quaternary glaciation where soils have not yet been sufficiently saturated with postglacial air-borne oceanic iodine As Hercus [1301] himself remarks in reference to the distribution of simple goitre in New Zealand "Speaking generally, our immature, recently deposited soils predispose to the development of goitre, and all parts of New Zealand can be said to be goitrous" Secondly, the digression affords an opportunity to put on record that due recognition has not apparently been given to the fact that it was an Australian medical officer, Harvey Sutton,[1331] who in

FIG 7 SOUTH-EAST AUSTRALIA, TASMANIA AND NEW ZEALAND



The red hatching indicates the areas where endemic goitre has been found

the course of goitre studies in New South Wales and Victoria was the first to notice and explain correctly the relationship between rainfall and goitre incidence, and to offer a reason why iodine is preferentially fixed in upper soil layers rather than in the deeper horizons of the same profile.

His accurate assessment of what happens during an important phase of the iodine cycle is characteristic of other similar investigations in Australasian countries. No peoples have faced the goitre menace with more efficiency and more energy, and none are nearer its final conquest Thanks to Hercus and his school, New Zealand's contribution to local iodine knowledge is fuller than that of probably any other country; and it is not difficult to predict that the recent elucidation by Clements & Wishart[1314] of the goitrogenic influences operative in parts of Tasmania will always rank among the classic researches in this field.

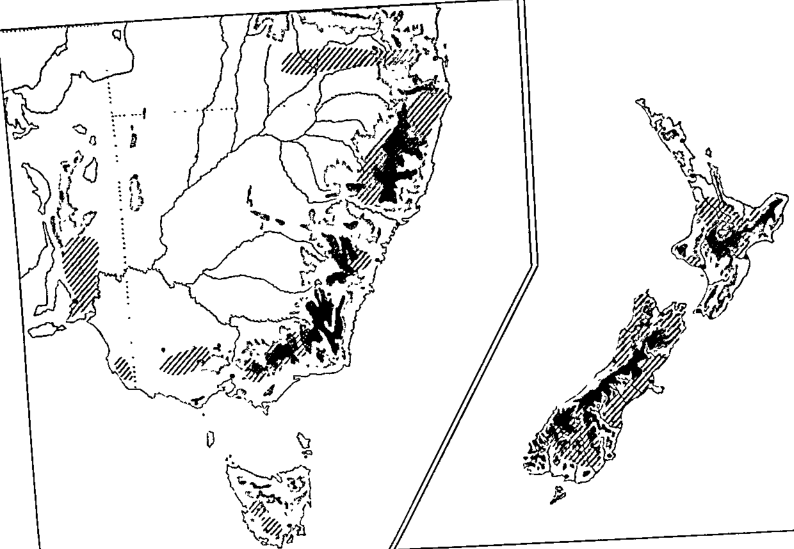
New Guinea

Politically, the island of New Guinea is divided into West New Guinea and the Territory of Papua and New Guinea, which is a United Nations Trust Territory administered by Australia Running the whole length of the country from west to east is a central mountain backbone with peaks rising to between 12 000 and 16 000 feet (3500 and 5000 m) Lying off the east of New Guinea are the islands of New Britain and New Ireland, which form part of the Territory of Papua and New Guinea Also belonging to the group are the Admiralty Islands, including Manus island, and the two northernmost Solomon Islands, namely, Bougainville and Buka

The distribution of goitre throughout the New Guinea islands is patchy Noosten[1159] mentions three affected localities in West New Guinea—namely, the region around Doreh Bay at the north-east corner of Vogelkop, the Timorini area, and the banks of the river Digoel in the south-east of the country In the territories to the east under Australian mandate, known goitre centres are a village close to Mount Toma about 30 miles from Rabaul in New Britain, a collection of villages in the Hydrographers' Range on the north-east coast of Papua near Buna; and a group of Papuan villages situated in the mountainous country at the head-waters of the Angabunga river about 40 miles inland from the coastal area west of Port Moresby

The last-named focus was discovered by Clements[1305] during a medical survey in the western portion of the Central Division of Papua undertaken for the Papuan Administration in 1935 Here, Clements saw no goitre among the Roro tribe on the coast, or among the subcoastal Mekeo tribe, who inhabit a dozen or so villages scattered at irregular intervals inland along the banks of the Angabunga river. But, higher up, at an altitude of about 6000 feet (2000 m) under the shadow of Mount Edward Albert, the highest peak in the Owen Stanley Range, he found chronic parenchymatous goitre in four villages—Ikuwei, Maini, Kailape and Tura

FIG 7. SOUTH-EAST AUSTRALIA, TASMANIA AND NEW ZEALAND



The red hatching indicates the areas where endemic goitre has been found

the course of goitre studies in New South Wales and Victoria was the first to notice and explain correctly the relationship between rainfall and goitre incidence, and to offer a reason why iodine is preferentially fixed in upper soil layers rather than in the deeper horizons of the same profile

His accurate assessment of what happens during an important phase of the iodine cycle is characteristic of other similar investigations in Australasian countries. No peoples have faced the goitre menace with more efficiency and more energy, and none are nearer its final conquest Thanks to Hercus and his school, New Zealand's contribution to local iodine knowledge is fuller than that of probably any other country; and it is not difficult to predict that the recent elucidation by Clements & Wishart [1218] of the goitrogenic influences operative in parts of Tasmania will always rank among the classic researches in this field

New Guinea

Politically, the island of New Guinea is divided into West New Guinea and the Territory of Papua and New Guinea, which is a United Nations Trust Territory administered by Australia Running the whole length of the country from west to east is a central mountain backbone with peaks rising to between 12 000 and 16 000 feet (3500 and 5000 m) Lying off the east of New Guinea are the islands of New Britain and New Ireland, which form part of the Territory of Papua and New Guinea. Also belonging to the group are the Admiralty Islands, including Manus island, and the two northernmost Solomon Islands, namely, Bougainville and Buka

The distribution of goitre throughout the New Guinea islands is patchy Noosten [1159] mentions three affected localities in West New Guinea—namely, the region around Doreh Bay at the north-east corner of Vogelkop, the Timorini area, and the banks of the river Digoel in the south-east of the country. In the territories to the east under Australian mandate, known goitre centres are a village close to Mount Toma about 30 miles from Rabaul in New Britain; a collection of villages in the Hydrographers' Range on the north-east coast of Papua near Buna, and a group of Papuan villages situated in the mountainous country at the head-waters of the Angabunga river about 40 miles inland from the coastal area west of Port Moresby

The last-named focus was discovered by Clements [1205] during a medical survey in the western portion of the Central Division of Papua undertaken for the Papuan Administration in 1935. Here, Clements saw no goitre among the Roro tribe on the coast, or among the subcoastal Mekeo tribe, who inhabit a dozen or so villages scattered at irregular intervals inland along the banks of the Angabunga river. But, higher up, at an altitude of about 6000 feet (2000 m) under the shadow of Mount Edward Albert, the highest peak in the Owen Stanley Range, he found chronic parenchymatous goitre in four villages—Ikuwei, Maini, Kailape and Tura.

Distribution is highly localized Other villages high on the mountain sides, *in apparently similar positions to those affected*, were found to be free from goitre, and within the goitrous villages themselves many people have continuously drunk water from the same source as the goitred people without contracting the disease The malady is confined to adults, the great majority of sufferers being women Onset is associated with first pregnancy and no woman becomes pregnant after having developed a thyroid enlargement—a feature, Clements remarks, unusual in a population with a high birth-rate The natives believe that in women goitre is the result of eating pig during the period of pregnancy, many pigs are eaten in a feast which may last a month Diets excessively rich in protein and fat are among the many that have been branded as goitrogenic, if this be true, a month's feast which includes a high proportion of pig fat might well impose an unaccustomed thyroid stress, especially during pregnancy

Profoundly stimulated by Clements' findings, McCullagh[1307] put forward his plan for the extinction of goitre in New Guinea To his energetic and refreshing action the Territory owes the initiation and development of a novel preventive form—one which might with advantage be followed in other regions of the world similarly placed

McCullagh confirms earlier views on the wide distribution of goitre throughout the Territory—extending from the border between the Dutch and British halves of Guinea in the west to the tip of Bougainville, the northernmost island of the Solomon group, far to the east. He estimates that at least one-third of the 300 000 people who live in the goitre areas and are thus exposed to goitrogenic influences, whatever they may be, actually develop the disease

McCullagh's revolutionary but wholly practical preventive method is depot injection of iodized oil Apparently it is not administratively possible to spread iodized salt easily throughout the affected areas—" To achieve this over all the years of pre-adult and early adult life would be a difficult task " Instead, from the results of an investigation in Melbourne, McCullagh advocates a single injection (one millilitre) of iodized oil to " provide a continuous supply of iodine over a period of two years " With larger volumes it may be possible to establish depots lasting up to five years An extensive anti-goitre campaign with iodized oil as first defence is now under way Evaluation of its effectiveness will be made known in 1960.

Around Hollandia, on the north-east coastal margin of Netherlands New Guinea, goitre is recognized as a problem among goats Sheep are only slightly affected The goitrous condition responds to the administration of potassium iodide through drinking-water (Zwart [1308])

Australia and Tasmania

Systematic goitre surveys in Australia are relatively few in number and in any case have been directed to areas already known to be or suspected

of being goitrous. As more surveys are undertaken it is possible that other goitre regions will be uncovered The disease has not been recorded among the aborigines, either formerly or at the present time Soon after the arrival of the first white settlers, the aboriginal peoples moved out of districts now recognized as goitrous and are today living in apparently non-goitre areas, for the disease has not been observed among them (Clements [1309])

Queensland

Reports by school medical officers suggest that the town of Cairns in the north of Queensland, and parts of the Atherton Plateau, which lies directly to the south-west of the town, are mildly goitrous The prevalence rate is unknown, however (Sutton [1331]) There are rumours of occurrence in the country between Toowoomba and Cunnamulla 200 to 300 miles west of Brisbane, but there is no official confirmation of this

New South Wales

Examination of 75 000 children in rural districts and an additional 10 000 in towns (Sutton [1330, 1331]) revealed considerable areas of goitrous country in the Great Dividing Range, which runs down the eastern part of New South Wales from the Queensland border in the north to the border of Victoria in the south These areas lie in several large river valleys, particularly the populous Hunter river valley, and in fertile plateaux throughout the range The percentage rates (given in parentheses for boys and girls respectively) were highest in such places as Grafton near the north-east coast (0 42, 4 35), Armidale in the New England Range (0.76, 3 57), Tamworth at the head of the river Namoi (6 33, 12.0) and Muswellbrook in the Hunter valley (5 5, 11 27)

Excluding the town of Grafton already mentioned, the incidence is less marked in the extreme north-east corner of the State, that is, in an area bounded by Wallangarra, Armidale, Coff's Harbour and Tweed Heads To the south, in the area bounded by Bathurst, Albury, Eden and Wollongong—but excluding Canberra—incidence is comparatively slight There is a small endemic area between Camden and Yerranderie, 50 miles to the west of Sydney A map showing the relative prevalence of goitre in these different sections of New South Wales is given by Sutton [1330] Among children at two schools in the Sydney suburb of Bondi, Clements [1310] found an over-all thyroid enlargement, palpable or visible, of 7 9% in boys and 17 3% in girls

Canberra

In 1947, the city of Canberra was found to be in a goitrous area A survey by Clements [1310] revealed the rates shown in Table XXIII among boys and girls in three age-groups between 6 and 14 years It is seen that the prevalence is higher in girls than in boys, particularly in the 12-14 years' age-group.

TABLE XXIII PREVALENCE OF THYROID ENLARGEMENT AMONG CHILDREN IN CANBERRA

Age-group	6-8 years				9-11 years				12-14 years			
Sex	boys		girls		boys		girls		boys		girls	
Number examined	177		186		198		160		177		164	
	number	%	number	%	number	%	number	%	number	%	number	%
Thyroids												
palpable	22	12.4	41	22.0	49	24.7	59	36.9	50	28.2	61	37.2
visible	8	4.5	10	5.4	11	5.6	16	10.0	9	5.1	37	22.5
Total	30	16.9	51	27.4	60	30.3	75	46.9	59	33.3	98	59.7

Shortly after the foregoing facts came to light, an iodine prophylaxis project was started in Canberra under the sponsorship of the Australian Department of Health The scheme consisted of administering to pregnant and lactating women, infants, children and adolescents, once a week, a *tablet containing 10 mg of potassium iodide The tablets were distributed* through infant welfare centres and schools. The results over five years have been reviewed by Clements;[1303, 1311] Table XXIV shows the percentage rate of visible goitre among Canberra children in the 9-11 age-group at each successive examination.

TABLE XXIV PREVALENCE OF VISIBLE GOITRE AMONG CANBERRA CHILDREN IN 9-11 AGE-GROUP AFTER INTRODUCTION OF IODINE PROPHYLAXIS

Year	Boys		Girls	
	number examined	percentage with visible goitre	number examined	percentage with visible goitre
1947	198	5.6	160	10.0
1948	236	2.1	215	5.0
1951	140	0	124	0
1952	299	0	281	1.7

In 1951, results from one school were not available, and in 1952 the survey was limited to children who had resided in Canberra for the previous three years Nevertheless, the incidence throughout shows a marked downward trend and the results clearly demonstrate the effectiveness of this method of goitre prevention and its suitability for infants and young children whose intake of iodized table-salt would at that age be negligible.

Regarding goitre prevention in Canberra, Hipsley[1320] has drawn attention to the convenience of adding iodized salt to bread at the time of baking,

TABLE XXV. PREVALENCE OF THYROID ENLARGEMENT AMONG CHILDREN IN GIPPSLAND

Age-group	6-8 years				9-11 years				12-14 years			
Sex	boys		girls		boys		girls		boys		girls	
Number examined	172		147		120		119		61		72	
	number	%	number	%	number	%	number	%	number	%	number	%
Thyroids,												
palpable	40	23.2	45	30.6	35	29.2	34	28.6	17	27.9	17	23.6
visible	23	13.4	25	17.0	21	17.5	30	25.2	8	13.1	30	41.7
Total .	63	36.6	70	47.6	56	46.7	64	53.8	25	41.0	47	65.3

as has been customary in the Netherlands since 1943 The method has recently been adopted in Canberra and now replaces the distribution of iodide tablets to schoolchildren and to expectant and nursing mothers.

Victoria

Gippsland, the wide littoral area lying between the mountains and the sea at the south-eastern end of Victoria, is the home of goitre in this State. Starting at Melbourne and moving eastwards through Gippsland for about 200 miles one would find goitre in the following succession of closely neighbouring towns and hamlets: Dandenong, Noojee, Warragul, Leongatha, Traralgon, Walhalla, Sale, Bairnsdale, Stratford, Bruthen in the Tambo valley, and Buchan and Orbost in the valley of the river Snowy. The districts of Dargo and Omeo in the Bowen Mountains to the north of Gippsland, where rainfall is heavy and frequent, are also affected

Prevalence is comparatively heavy In Bairnsdale, one of the chief towns of Gippsland, rates of 20% to 33% in boys and of 32% to 47% in girls were recorded by Summons [1329] in 1927. Of 14 boys between the ages of 12 and 14 attending the junior technical school at Sale, 8 had goitre. Clements' more recent Gippsland figures (1948),[1310] given in Table XXV, show little, if any, improvement on the earlier ones.

It will be noticed that the maximum rate in boys is in the 9-11 years' age-group, whilst in girls maximum intensity occurs between 12 and 14 years of age

On the other side of Victoria to the west of Melbourne goitre is much less evident, but minor occurrences have been noted in scattered and localized areas around Ballarat, Geelong, Colac, Bendigo, Ararat, Hamilton and Warrnambool.

South Australia

The only endemic goitre area in the State of South Australia lies in the Adelaide Hills, part of the Mount Lofty Range to the east of Adelaide.

TABLE XXIII. PREVALENCE OF THYROID ENLARGEMENT AMONG CHILDREN IN CANBERRA

Age-group	6-8 years				9-11 years				12-14 years			
Sex	boys		girls		boys		girls		boys		girls	
Number examined	177		185		198		160		177		164	
	number	%	number	%	number	%	number	%	number	%	number	%
Thyroids												
palpable	22	12.4	41	22.0	49	24.7	59	36.9	50	28.2	61	37.2
visible	8	4.5	10	5.4	11	5.6	16	10.0	9	5.1	37	22.5
Total	30	16.9	51	27.4	60	30.3	75	45.9	59	33.3	98	59.7

Shortly after the foregoing facts came to light, an iodine prophylaxis project was started in Canberra under the sponsorship of the Australian Department of Health. The scheme consisted of administering to pregnant and lactating women, infants, children and adolescents, once a week, a tablet containing 10 mg of potassium iodide. The tablets were distributed through infant welfare centres and schools. The results over five years have been reviewed by Clements;[1303, 1311] Table XXIV shows the percentage rate of visible goitre among Canberra children in the 9-11 age-group at each successive examination

TABLE XXIV PREVALENCE OF VISIBLE GOITRE AMONG CANBERRA CHILDREN IN 9-11 AGE-GROUP AFTER INTRODUCTION OF IODINE PROPHYLAXIS

Year	Boys		Girls	
	number examined	percentage with visible goitre	number examined	percentage with visible goitre
1947	198	5.6	160	10.0
1948	236	2.1	215	5.0
1951	140	0	124	0
1952	299	0	281	1.7

In 1951, results from one school were not available, and in 1952 the survey was limited to children who had resided in Canberra for the previous three years. *Nevertheless, the incidence throughout shows a marked downward trend and the results clearly demonstrate the effectiveness of this method of goitre prevention and its suitability for infants and young children whose intake of iodized table-salt would at that age be negligible.*

Regarding goitre prevention in Canberra, Hipsley[1320] has drawn attention to the convenience of adding iodized salt to bread at the time of baking.

TABLE XXVI. PREVALENCE OF VISIBLE GOITRE AMONG CHILDREN IN TASMANIA BEFORE AND AFTER IODINE PROPHYLAXIS

Age-group (years)	Sex	1949 survey		1954 survey	
		number examined	percentage with visible goitres	number examined	percentage with visible goitres
5	M	217	0	675	5 03
6-8	M	1218	1.39	3286	8 12
9-11	M	1376	3 71	2762	9 02
12-14	M	1180	6 44	2727	9 90
15-17	M	190	3 5	444	3 85
5	F	184	2 7	694	5 90
6-8	F	1259	3 1	3099	9 61
9-11	F	1364	8 51	2733	12 58
12-14	F	1675	20 8	3344	16 74
15-17	F	253	23 3	535	22 99

TABLE XXVII. PREVALENCE OF VISIBLE GOITRE AMONG CHILDREN IN TASMANIA, FOR EACH YEAR OF AGE FROM 5 TO 8 IN 1954 SURVEY

Age (years)	Boys		Girls	
	number examined	percentage with visible goitres	number examined	percentage with visible goitres
5	242	7 8	303	8 2
6	489	10 0	486	11 1
7	546	11 7	550	11 4
8	460	10 8	450	12 2

Table XXVII) were similar, this is in marked contrast to the results obtained in the 1949 survey, when there was a substantial difference in prevalence between boys and girls, and steep increases from the youngest children to the older age-groups The 1949 pattern of prevalence was similar to that observed in other Australian surveys

To find an explanation for these unexpected rises in prevalence during a five-year iodine regime, the reliability of the standards of diagnosis was checked and confirmed, the efficiency of the system of tablet distribution was verified, and the over-all prevalence figures for 1949 and 1954 were subjected to mathematical analysis and re-study district by district

When in this way the country was partitioned into six districts and data were related strictly to the districts in which they had been gathered, and

This closely settled farming region extends to about half a million acres (200 000 ha) and has a population of approximately 20 000 Jungfer,[1321] who supervised a child health survey in the area, found a general goitre rate in the " 10 years and over " age-group of 21 1% among girls and 4.1% among boys The rates were somewhat higher (26.6% and 11.1%, respectively) in a selected group of " ten-plus " children who had been born in the Adelaide Hills and had been permanently resident there up to the time of Jungfer's survey.

Western Australia

" *Goitre is not a problem of any importance in Western Australia Hospital records show very few cases and no evidence of endemic areas in the State* " *This statement by the Commissioner of Public Health (1943) is confirmed by Clements,*[1303] *who writes that despite a deliberate search for goitre in the south-western corner of the State where a number of trace-element deficiency diseases occur in animals, endemic goitre has not been recorded*

Northern Territories

There are no reports of goitre occurrence in the Northern Territories of Australia

Tasmania

Practically the whole of Tasmania is goitrous The disease has been known in the island since the last century, but the first serious study of the problem was not made until *1949*, when *Clements examined 8000 school-children and found visible goitres in approximately 6% of boys and 20% of girls in the age-group 12-14 years He also noted that at least 20 in every 100 adult women had a goitre, and pointed out that the annual death-rate from thyrotoxicosis in Tasmania had been significantly higher than the Australian average for at least 70 years.*[1312, 1316]

Accepting world experience that endemic goitre is due to inadequate dietary iodine intake, and following the Canberra precedent noted above, Clements succeeded in promoting a preventive scheme whereby tablets, each containing 10 mg of potassium iodide, were distributed by the health authorities to all children up to the school-leaving age of 16 years In 1954, five years after the prophylactic procedure was introduced, a second survey was made to determine its effects This involved the examination of some 20 300 children between the ages of 5 and 17 years As may be seen from Tables XXVI and XXVII, the results were almost entirely contrary to expectations.

In the first place, the 1954 survey showed a marked increase in goitre prevalence among both boys and girls in each age-group, with the exception of girls 12-14 and 15-17 years of age. Secondly, the goitre rates for each year of age in both boys and girls from 5 to 8 years in the 1954 survey (see

experimentally to humans and to laboratory animals clearly interfered with their [131]I uptake; and the fact that marked thyroid hyperplasia developed in calves born of cows which had been fed on chou-moellier. Evidence was also forthcoming that milk containing a goitrogen could be produced by cows grazing on pastures heavily contaminated with certain cruciferous weeds.

Final proof of the hypothesis set up by Clements & Wishart [1316] requires the actual isolation of the goitrogenic substance from milk and a demonstration of its anti-thyroid potency on human subjects Nevertheless, their findings are more than indicative that much of the goitre in Tasmania is due to goitrogenic interference with a vital step in the synthesis of thyroxine which cannot be overcome by iodine administration Clements & Wishart are careful to stress, however, that this does not affect the fact that a large amount of the goitre endemic in Tasmania and elsewhere in Australia is due to straightforward iodine deficiency and is therefore amenable to iodine preventive measures

Such was the position in 1956 Since then, a systematic investigation of the thioglycosides (and their aglycones) of chou-moellier and of cruciferous weeds prevalent as contaminants of pastures in goitrous areas of Tasmania and southern Queensland has been made by Bachelard & Trikojus [1309] in association with the Goitre Sub-Committee of the National Health and Medical Research Council They have succeeded in isolating a substance called cheiroline (γ-methylsulphonyl-propyl-*iso*thiocyanate) from the fruit and leaves of turnip weed (*Rapistrum rugosum*) and, by experiments on rats, have proved it to be goitrogenic. Further work is in progress to determine whether this and other *iso*thiocyanates can be absorbed and transferred to the milk of cows grazing on pastures contaminated with cruciferous weeds

Turnip weed (*Rapistrum rugosum*) grows profusely around Warwick in southern Queensland and it is interesting that endemic goitre among children in this area occurs only in the valleys where turnip weed is prolific Comparatively large doses of potassium iodide (10 mg twice weekly) are without effect upon epidemic goitre caused by goitrogens of this type. Administration of thyroid substance is the preferred therapeutic method (Clements [1315])

On the question of prophylaxis and treatment, an observation by Clements [1314] remains unexplained. Following the detection of goitre among children at Hopewood House, Bowral, south-west of Sydney, a number of changes were suggested in the dietary regime, including the substitution of iodized salt for powdered kelp which had been given on account of its iodine content and as the sole source of sodium chloride At the next examination, some six months after the change, a noticeable reduction in the size of the enlarged thyroids was seen Experiments to determine whether the kelp contained a goitrogenic substance proved negative

not lumped with others for the island as a whole, it was found that in three districts there had been a general fall in prevalence since 1949, proving that iodine had been effectively doing its work, but that in two, or possibly three, other areas there had been a steep rise. The over-all rise in prevalence seen in the figures as a whole was due to the sharp rises in these three individual areas. The district-by-district analysis of data also confirmed the improved rates among older girls, and established that the higher rate among young children in 1954, as compared with 1949, was real and not due to some error of diagnosis or irregularity in the distribution or altered potency of the iodide tablets. This feature remained the most remarkable of the 1954 survey.

These findings led Clements & Wishart [1315] to consider the possibility that there might be two causes of goitre in Tasmania—a straightforward iodine deficiency operative in some districts and a goitrogenic agency predominant in others Strong support for the goitrogen hypothesis was *found in two interrelated sets of circumstances. In 1950, just one year after* prophylaxis by iodide tablets began in Tasmania, the Commonwealth Government introduced a free-milk scheme for schoolchildren to stimulate milk consumption throughout Australia for health reasons To meet the increased demand for milk occasioned by this scheme, particularly in the autumn and winter months when cows are usually dried-off, farmers were obliged to keep their herds in production all the year round. Accordingly, they extended their plantings of chou-moellier (*Brassica oleracea* var. *acephala*, marrowstem kale), a crop available for direct grazing through the winter months when grass is burnt off by frost

Between the years 1948 and 1953 the area in Tasmania sown to chou-moellier increased from 83 acres (34 ha) to 235 acres (95 ha) and the quantity of chou-moellier and kale seed sold in the country during these same six years increased from 23 7 to 214 9 hundredweights (from about 12 to 110 quintals) The districts where chou-moellier cultivation increased most were found to correspond exactly with those where goitre incidence had increased between the 1949 and 1954 surveys

Chou-moellier belongs to the Brassica genus, members of which may contain the goitrogen L-5-vinyl-2-thio-oxazolidone. Since the goitrogenic activity of this substance may be destroyed by heat, and since all vegetables of the *Brassica* genus eaten directly by Tasmanians are cooked, Clements & [illegible]

for their point of view. This included the fact that the rise in goitre rates among young children coincided with their increased consumption of milk under the free-milk scheme; *the fact that regular weekly doses of 10 mg* of potassium iodide failed to prevent the development of goitre in these children; the fact that milk from chou-moellier-fed cows administered

experimentally to humans and to laboratory animals clearly interfered with their ^{131}I uptake, and the fact that marked thyroid hyperplasia developed in calves born of cows which had been fed on chou-moellier. Evidence was also forthcoming that milk containing a goitrogen could be produced by cows grazing on pastures heavily contaminated with certain cruciferous weeds

Final proof of the hypothesis set up by Clements & Wishart [1316] requires the actual isolation of the goitrogenic substance from milk and a demonstration of its anti-thyroid potency on human subjects. Nevertheless, their findings are more than indicative that much of the goitre in Tasmania is due to goitrogenic interference with a vital step in the synthesis of thyroxine which cannot be overcome by iodine administration. Clements & Wishart are careful to stress, however, that this does not affect the fact that a large amount of the goitre endemic in Tasmania and elsewhere in Australia is due to straightforward iodine deficiency and is therefore amenable to iodine preventive measures

Such was the position in 1956 Since then, a systematic investigation of the thioglycosides (and their aglycones) of chou-moellier and of cruciferous weeds prevalent as contaminants of pastures in goitrous areas of Tasmania and southern Queensland has been made by Bachelard & Trikojus [1309] in association with the Goitre Sub-Committee of the National Health and Medical Research Council They have succeeded in isolating a substance called cheiroline (γ-methylsulphonyl-propyl-*iso*thiocyanate) from the fruit and leaves of turnip weed (*Rapistrum rugosum*) and, by experiments on rats, have proved it to be goitrogenic. Further work is in progress to determine whether this and other *iso*thiocyanates can be absorbed and transferred to the milk of cows grazing on pastures contaminated with cruciferous weeds

Turnip weed (*Rapistrum rugosum*) grows profusely around Warwick in southern Queensland and it is interesting that endemic goitre among children in this area occurs only in the valleys where turnip weed is prolific Comparatively large doses of potassium iodide (10 mg twice weekly) are without effect upon epidemic goitre caused by goitrogens of this type Administration of thyroid substance is the preferred therapeutic method (Clements [1315])

On the question of prophylaxis and treatment, an observation by Clements [1314] remains unexplained Following the detection of goitre among children at Hopewood House, Bowral, south-west of Sydney, a number of changes were suggested in the dietary regime, including the substitution of iodized salt for powdered kelp which had been given on account of its iodine content and as the sole source of sodium chloride At the next examination, some six months after the change, a noticeable reduction in the size of the enlarged thyroids was seen Experiments to determine whether the kelp contained a goitrogenic substance proved negative.

Animal goitre in Tasmania

An outbreak of congenital goitre in lambs on alluvial river flats in the Huon valley south of Hobart was reported by Southcott [1326] in 1945. Since then occurrences have been noted in the Derwent valley and at several places in the southern midlands Goitre also appears to be prevalent among farm horses in Tasmania, and occasional cases suggestive of iodine deficiency have been seen in calves in various districts (Green [1317])

New Zealand

Goitre is endemic in both the North and South Islands and affects Maoris and Europeans alike There is a tradition that the malady was in evidence among the Maori peoples long before the beginnings of British settlement; their language has for many generations contained the word "tenga" (sometimes "tena") meaning goitre [1331, 1335] Among European colonists the disease was first mentioned in 1882 by C Nedwill (cited by Hercus [1345]) who noticed its frequency in and around Christchurch In 1889 (invariably given wrongly as 1888), Hacon [1343] recorded the widespread occurrence of goitre throughout the Provincial District of Canterbury, and from inquiries conducted in 1910 Colquhoun [1337] concluded that the whole country was goitrous Greenwald [1312] asserts that no credible evidence exists that goitre was a disease in New Zealand before the advent of Europeans He adduces this as sound argument against the generally accepted modern view that endemic goitre is a consequence of environmental iodine deficiency

Medical inspection of recruits during the 1914-1918 war, when 1680 men out of 135 000 examined were rejected for active service on account of goitre, brought the problem more directly to public attention and systematic surveys were thereupon undertaken In 1920 Hercus & Baker [1318] examined 15 000 schoolchildren in the age-group 5 to 12 years in Canterbury and Westland (South Island) to find 32% with markedly enlarged thyroid glands and a further 29% with glands sufficiently palpable and visible on deglutition to constitute pathological enlargement This preliminary survey was later greatly extended to cover many thousands of children in both the North and South Islands and medical examination was coupled with chemical determinations of iodine in a large number of representative soils and waters collected throughout the entire Dominion (Hercus and co-workers; [1344, 1347, 1349, 1350, 1353, 1354] Shore & Andrew [1359, 1362]).

In these surveys the southern section of the South Island (Otago and Southland) showed an average goitre rate of 26% rising to 30% and 40% in the Taieri and Clutha valleys west and south-west of Dunedin In the central and northern portion of South Island (Canterbury, Nelson, Marlborough) the rate was much higher, exceeding 60% in South Canterbury and around Christchurch Observations at the government maternity

hospital in Christchurch revealed 60% of mothers with goitre and approximately 8% of babies born with thyroid enlargement, sometimes to a degree sufficient to interfere with normal flexion of the head at delivery.

The North Island Provincial Districts of Wellington, Taranaki and Hawke's Bay had an average goitre rate of 21%; there were black spots in the Hutt valley (41%) north-east of Wellington, and in the west coastal county of Wanganui, where the rate reached 46% Other fairly goitrous districts of the North Island were found in the mountainous parts of Auckland, where rates of 30% were recorded among schoolchildren in the Counties of Taupo and Rotorua, and in the Waikato and Piako valleys to the west of Rotorua. Shore & Andrew [1359] record rates of 47% in boys and 56% in girls at Gisborne Only New Plymouth in the west of Taranaki Provincial District, and the Thames and Coromandel peninsula in the north of Auckland, have rates under 10%

The iodine analytical determinations yielded data which fully sustain *the iodine-deficiency theory of causation* Though anomalies were encountered, the whole body of facts was too large and the inverse relationship between goitre prevalence and environmental iodine supply too consistent to be fortuitous. Broadly speaking, it was found that in New Zealand iodine is lowest and goitre highest on the recent alluvial soils of river valleys, on porous soils derived from siliceous volcanic rocks, and on marine sandstones and greensands—indeed, on all clayless sandy soils and gravels from which iodine is easily leached out by weathering By contrast, goitre is low and iodine high in regions underlain by igneous rocks (granite, basalt, andesite) yielding clayey soils and fertile brown or red loams rich in iodine

As a result of these exhaustive investigations, iodized salt was officially introduced into New Zealand on a voluntary basis in June 1924. At first the salt was inadequately fortified at a level of 1 part of potassium or sodium iodide in 250 000 parts of salt Three years later, wide and detailed inquiries in grocers' shops and in a representative sample of Canterbury homes revealed that of all salt bought for table and culinary purposes only 5% was of the iodized variety By 1934, following a vigorous educational campaign by the Department of Health, the proportion had risen to 30% In 1940, yielding to the pressure of enlightened medical opinion, the New Zealand Government raised the iodide standard to 1 part in 20 000 parts of salt, and the New Zealand Medical Research Council's Thyroid Research Committee recommended that salt iodized in this proportion should become the standard domestic salt of the country and that non-iodized salt should *be supplied only to people asking specifically for it* Although this policy has not yet been wholly adopted, approximately 80% of the population today use iodized salt of the 1 : 20 000 strength, at least at table

Despite the fact that the more potent salt (1 : 20 000) was not introduced until 1942, a notable decline in the prevalence of thyroid enlargement

among schoolchildren had already become apparent by that time. In 1951 Tolley [1364] made a survey of the children living in the South Canterbury and North Otago school areas with the object of comparing the prevalence among them with that found by Hercus and others 25 years previously. She found the average rate for both these districts to be 25%, as compared with 62% in 1925 The almost complete disappearance of gross goitrous enlargements accounted for most of this fall On the other hand, Tolley found that the number of "incipient" enlargements (i e., palpable and small visible goitres) was still relatively high, indeed somewhat higher than the 1925 figure. From this she concludes that either the iodine intake is still too low, even with salt iodized at the 1 : 20 000 level, or that some unknown factor is responsible.

Reviewing Tolley's results in the light of their own experience, Clements & Wishart [1316] suggest that the residues of incipient goitre may be due to the action of a goitrogenic substance of a character similar to that suspected to operate in Tasmania (see page 194). They recall that in New Plymouth, at one time regarded as virtually goitre-free, the rate of visible thyroid enlargement among children rose from less than 2% in 1927 to 53% in 1933 (Mecredy, [1356] Shore & Andrew [1361]). Chou-moellier, along with other species of *Brassica*, has been grown in and around New Plymouth for many years. It may well be that changes in the pattern and extent of *Brassica* cultivation, or of the cultivation of other possibly goitrogenic crops, have not been sufficiently investigated in relation to goitre occurrence in New Zealand.

Animal goitre in New Zealand

Domestic animals are not exempt from thyroid disease in New Zealand. Hercus [1315, 1319] has seen goitres, sometimes of large size, in sheep, cattle, *pigs and dogs—especially fox-terriers In racing stables cases have been* known of horses developing goitre during training Of particular interest has been the occurrence of epidemic thyroid enlargement in lambs [1338, 1339, 1355, 1363] Symptoms suggesting acute iodine deficiency among sheep led to serious loss of lambs in the Wanaka district of South Island in 1929. The trouble was overcome by means of iodized licks.[1355] More recently, a severe outbreak of goitre accompanied by heavy neo-natal mortality in lambs from kale-fed ewes has been described by Sinclair & Andrews.[1363] A few moderate cases were also observed among lambs from pasture-fed ewes, but these did not appear to be associated with unusual mortality In both pasture-fed and kale-fed groups goitre was prevented and the iodine status of the lamb thyroids raised by dosing the ewes with potassium iodide during pregnancy.

South Pacific Islands

Absolute proof that goitre can be endemic in an extreme maritime environment is found in the South Pacific. Proximity to the sea does not

necessarily protect all the peoples inhabiting the islands scattered throughout the 18 million square miles of ocean from the Marianas in the north to Norfolk Island and Pitcairn Island in the far south. The disease occurs in Fiji and cases have been reported from Tonga, Samoa and the Cook Islands.

Fiji Islands

A survey by members of the Otago Medical School, New Zealand, found goitre endemic in the valley of the Singatoka, the second largest river in the island of Viti Levu Many villages containing both Fijians and Indians are dotted along its banks, and simple goitre is endemic in both races, except in the Fijian villages near the mouth of the river where much sea-food is eaten (Hercus[1304]) L Wills (personal communications, 1950 and 1951) also reports "plenty of goitre all round the island in spite of fish and marine life in the menu" She saw many visibly enlarged thyroids among pregnant Fijian women

Growing concern at the apparently increasing goitre incidence among the Indian population in western and northern districts of the Colony has prompted the South Pacific Health Service to make iodate-fortified salt available in Fiji

Tonga or Friendly Islands

According to the Chief Medical Officer[1365] and to Simmons,[1369] Tongans exhibit a certain amount of goitre which points to iodine deficiency Some fish is eaten but not a quantity large enough to supply the full iodine requirement.

Samoa and the Cook Islands

Occasional sporadic cases of simple goitre have been reported from Samoa and the Cook Islands, but the incidence is so low as to merit the term goitre-free being applied to these islands (Hercus[1304]). In a thorough nutrition survey of 365 Cook Islanders of all ages chosen at random in 66 family groups from the village of Arorangi on the island of Rarotonga, Faine & Hercus[1366] noted only one mild case of thyroid enlargement, the large consumption of fish and sea-foods must provide a sufficiently high iodine intake

Hawaiian Islands

Goitre is not endemic in the islands of the Hawaiian group, nevertheless, the non-toxic nodular variety is by no means rare Examination of hospital records by Freeman[1367] revealed this type of goitre in more than 25% of 423 patients who had undergone thyroid surgery at The Clinic, Honolulu, during the twenty years to 1950

Several studies have shown that there is sufficient iodine in drinking-water and local foods in Hawaii to prevent thyroid disorders that might

result from lack of iodine. A conjecture that the high frequency of cleft palate in Hawaiian children might be associated with low metabolic rate in their mothers was proved by Henderson & Krantz [1368] to be unfounded.

BIBLIOGRAPHY

General

1 Bircher, H (1883) *Der endemische Kropf und seine Beziehungen zur Taubstummheit und zur Cretinismus*, Basel
2. Chile, Oficina Educacional del Yodo (1950) *El bocio en la América Latina*, Santiago de Chile
3 Chilean Iodine Educational Bureau (1946) *World goitre survey*, London
4 Clemow, F G (1903) *The geography of disease*, Cambridge, pp 170-179
5 De Quervain, F & Wegelin, C (1936) *Der endemische Kretinismus*, Berlin & Wien
6 Eggenberger, H (1928) In. *Handbuch der inneren Sekretion*, Leipzig, vol 3, part I, pp 684-958
7. Greenwald, I (1945) *Bull Hist Med*, **17**, 229
8 Hirsch, A (1860-64) *Handbuch der historisch-geographischen Pathologie*, Erlangen
9 McCarrison, R (1913) *The etiology of endemic goitre*, London
10 McClendon, J F (1939) *Iodine and the incidence of goiter*, Minneapolis
11 Pfluger, H (1937) *Dtsch Arch klin Med*, **180**, 212
12 Saint-Lager, J (1867) *Etudes sur les causes du crétinisme et du goitre endémique*, Paris, Baillière

Canada

13. Abbott, A C (1932) *Canad med Ass. J*, **27**, 8, 146, 236, 376
14 Adami, J G (1900) *Montreal med J*, **29**, 1
15 Adamson, J. D et al (1945) *Canad med Ass J*, **52**, 227
16 Binning, G (1935) *Canad med Ass J*, **32**, 533
17 Binning, G (1939) *Canad publ Hlth J*, **30**, 393
18 Edward, J F (1948) *Canad med. Ass J*, **58**, 210
19 Hamilton, T G & McRae, D. F (1925) *Canad med Ass. J*, **15**, 1017
20. Hector, J (1863) In *Journals, detailed reports, and observations relative to the exploration of British North America by Captain Palliser during the years 1857-1860*, London, p 78
21 Jackes, H L (1941) *Canad med Ass J*, **45**, 142
22. Keith, W D (1924) *Canad med Ass J*, **14**, 284
23. MacDermot, J H (1949) *Canad. med. Ass. J*, **61**, 177
24 Richardson, J (1823) *Narrative of a journey to the shores of the polar sea, by John Franklin*, London, pp 118-119
25. Shepherd, F J (1919) *Goitre its incidence, course, causation, prophylaxis and treatment*, Ottawa
26. Simpson, G (1847) *Narrative of a journey round the world, during the years 1841 and 1842*, London, vol 1, p 118
27 Springle, J A (1899) *Montreal med J.*, **28**, 909
28 Vivian, R. P. et al (1948) *Canad. med Ass J*, **59**, 505
29. Walker, O J (1932) *Canad J. Res*, **7**, 137

United States of America

30 Adolph, W. H. & Prochaska, F J (1929) *J. Amer. med Ass*, **92**, 2158
31. Altland, J K. & Brush, B E (1952) *J. Mich med Soc.*, **51**, 985

32. Brush, B E. & Altland, J. K (1952) *J. clin Endocr*, **12**, 1380
33 Cavanagh, C R., jr (1958) *J Amer med Ass*, **167**, 2053
34 Daft, F. S (1958) *Fed. Proc.*, **17**, 740
35 Darby, W J et al (1956) *J Nutr*, **60**, Suppl. No 2
36 Foote, R F (1955) *West J Surg.*, **63**, 497
37. George, J C & Flory, D. W (1956) *Sth med. J*, **49**, 1410
38 *Greenwald, I (1949) Fed Proc*, **8**, 384
39 Greenwald, I. (1955) *J Hist Med*, **10**, 277
40 *Grollman, A & Gryte, C F. (1944) J clin. Endocr*, *4*, *440*
41 Hamwi, G J (1955) *Ohio's Hlth*, **8**, No. 4, p 1
42 Hamwi, G J et al (1955) *Amer. J publ. Hlth*, **45**, 1344
43 Hull, O H (1955) *Arch. Path Lab Med.*, **59**, 291
44 Johnson, W O (1929) *Amer. J publ Hlth*, **19**, 1090
45 Jordan, R A & Canuteson, R. I (1948) *J.-Lancet*, **68**, 241
46 Kenyon, F, Kelly, H J & Macy, I G. (1954) *J Amer diet Ass*, **30**, 987
47 Kimball, O P (1953) *Bull Wld Hlth Org*, **9**, 241
48 Mahorner, H (1944) *Surgery*, **16**, 764
49. Mahorner, H & Barrow, W (1939) *Trans Amer Ass Stud Goiter*, p. 297
50 Marine, D (1954) *Ann intern Med*, **41**, 875
51 Miller, J M (1955) *New Engl. J Med*, **252**, 247
52 Olesen, R (1929) *Publ Hlth Bull (Wash)*, No. 192
53 Olesen, R (1933) *Bull Off int Hyg. publ*, **25**, 1961
54 Pennington, W. H (1942) *Sth Surg*, **11**, 490
55 Phillips, C (1939) *Tex St J Med*, **34**, 688
56 Phillips, J T, jr (1954) *Va med. Mon*, **81**, 386
57 Richards, R (1929) *Amer J Surg*, **7**, 44
58 Rowntree, L G (1944) *J clin. Endocr*, **4**, 545
59 Starr, P (1958) *Postgrad Med*, **24**, No 2

Mexico

60 Chávez Montes, J (1957) *Pren méd mex*, **22**, 129
61 Greenwald, I (1959) *Tex Rep Biol Med*, **17**, 467
62 Stacpoole, H H (1953) *Bull Wld Hlth Org*, **9**, 283
63 Stacpoole, H H (1958) *Bol epidem (Mex)*, **22**, 29
64 Stacpoole, H H (1958) *Bol epidem (Mex)*, **22**, 31

Central America (general)

65 Cabezas, A, Pineda, T & Scrimshaw, N S (1953) *Amer J. publ Hlth*, **43**, 265
66 Holman, J C & Góngora y Lopez, J (1955) *Bol Ofic sanit. panamer*, **38**, 57
67 Scrimshaw, N S. (1954) *Bol Ofic. sanit panamer*, **36**, 277

Guatemala

68 Borhegyi, S F & Scrimshaw, N S (1957) *Amer Antiq* **23**, 174
69 Borhegyi, S F & Scrimshaw, N S (1959) *Bol. Ofic sanit panamer*, Suppl No 3, p 157
70 Herrera C, J R (1939) *Bol sanit (Salvador)*, **10**, 232
71 Institute of Nutrition of Central America and Panama (1951) *Preliminary report on endemic goitre in Central America and Panama*, Guatemala
72. Kimball, O P (1953) *Ohio St med J*, **49**, 313
73 Mahorner, H (1951) *Trans Amer Goiter Ass.*, p. 299
74 Méndez, J et al (1953) *Fed. Proc*, **12**, 423
75. Muñoz, J A (1954) *Informe preliminar sobre la encuesta de bocio endemico practicada en todos los departamentos de la Republica de Guatemala*, Guatemala (Institute of Nutrition of Central America and Panama)

76. Muñoz, J A , Perez, C & Scrimshaw, N S (1955) *Amer. J trop. Med Hyg.*, 4, 963
77. Scrimshaw, N S et al (1953) *Lancet*, 2, 166

Honduras

78 Borjas, E A. (1955) *Rev méd hondureña*, 23, 957
79 Borjas, E A & Scrimshaw, N S (1954) *Amer J publ Hlth*, 44, 1411

El Salvador

80 Cabezas, A (1951) *Sanid. Salvador*, 2, 325
81. Cabezas, A (1952) *Sanid. Salvador*, 3, 116
82 Pineda M , T (1951) *Sanid Salvador*, 2, 318

Nicaragua

83 Arce Páiz, A (1956) *Bol Sanit Nicaragua*, 2, 300

Costa Rica

84. De Girolami, E & Fallas Díaz, M (1954) *Rev Biol trop (S José)*, 2, 1
85 García C , E. (1941) *Rev méd C Rica*, 4, 558
86 Perez, C et al. (1956) *Amer. J publ Hlth*, 46, 1283
87 Urcuyo G , C (1942) *Rev méd C Rica*, 5, 181

Panama

88 Reverte Coma, J M (1954) *Arch med panameñ*, 3, 121
89 Reverte Coma, J M. (1955) *Arch méd panameñ*, 4, 9
90. Reverte Coma, J M (1955) *Arch. méd panameñ*, 4, 45
91 Reverte Coma, J M (1955) *Arch méd panameñ.*, 4, 100
92. Reverte Coma, J M (1956) *Arch méd panameñ*, 5, 130
93 Reverte Coma, J M (1958-1959) *Bocio endémico en Panamá*, Panama

Cuba

94. Schutte, J A. et al (1958) *Arch cuban Cancer*, 17, 177

Dominican Republic

95. De Leon M., A (1944) In *Memoria del Congreso Médico Dominicano del Centenario*, Santiago, Santo Domingo, p 215
96 Purcell P , H S. (1944) In *Memoria del Congreso Médico Dominicano del Centenario*, Santiago, Santo Domingo, p 199

South America (general)

97 *Crotti, A (1938) Diseases of the thyroid, parathyroids and thymus*, 3rd ed , London, p 469
98 Greenwald, I (1957) *Tex Rep Biol Med*, 15, 874
99 Orr, W H (1948) *Northw. Med (Seattle)*, 47, 803

Colombia

100 [illegible] (19[illegible]) [illegible] 19, 41
101
102.
103 [illegible] *y curación de los cotos*
104
105 Góngora y López, J & Mejía [illegible] *(Bogotá)*, 16, 357
106. Góngora y López, J. & Young, N. (1949) *Quim. e Industr. (Bogotá)*, 1, Nos. 3-4, p 21

107. Góngora y López, J , Young, N & Iregui B , A (1950) *Rev Hig (Bogotá)*, 24, 291
108. Greenwald, I (1950) *J clin Endocr*, 10, 1309
109. Humboldt, A von (1824) *J Physiol. exp path*, 4, 109
110. Mutis, J C (1794) *Reflexiones sobre la enfermedad que vulgarmente se llama coto* In: *Papel periódico de Santafé de Bogotá*, No 137, pp 669-676
111 Parra, H (1948) *Amer. J publ. Hlth*, 38, 820
112. Parra, H (1948) *Rev colomb Pediat*, 8, 176
113 Parra, H. (1956) *Arch Pediat Urug*, 27, 204
114 Roulin, P (1825) *J Physiol exp path*, 5, 266
115 Socarrás, J F (1942) *An Econ Estadist colomb*, 5, 65
116. Thonnard-Neumann, E (1957) *Z Tropenmed Parasit*, 8, 367

Venezuela

117 Bengoa, J M (1946) *Medicina social en el medio rural Venezolano*, Caracas, pp 109-123
118 De Venanzi, F et al (1955) *Acta méd venez*, 3, 200
119 De Venanzi, F et al (1955) *Gac méd Caracas*, 63, 360
120 De Venanzi, F et al (1958) *Acta cient venez*, 9, 13
121 Gaede, K. et al (1957) *Acta cient venez*, 8, 129
122 García L , J V (1957) *Arch venez. Nutr*, 8, 107
123 Roche, M (1959) *J clin Endocr*, 19, 1440
124 Roche, M et al (1955) *J clin Endocr*, 15, 838
125. Roche, M et al (1955) *Rev Policlin Caracas*, 23, 213
126 Roche, M et al (1956) *Proc Soc exp Biol (N Y.)*, 91, 661
127. Roche, M et al (1957) *J clin Endocr*, 17, 99
128 Rodríguez, R O (1955) *Gac méd Caracas*, 62, 189
129 Rodriguez, R O (1956) *Gac méd Caracas*, 64, 169

Ecuador

130 Arcos, G. (1938) *An. Univ centr Ecuador*, 61, 599
131 León, L. A (1959) *Gac méd (Guayaquil)*, 14, 8
132 Sánchez, C R & Paredes, J E (1933) *An Univ centr Ecuador*, 50, 585
133. Tenorio, M J (1950) *Contribucion al estudio del bocio en el Ecuador*, Cuenca (Thesis)

Peru

134 Burga H , B (1938) *Reforma med*, 24, 967, 972, 986
135 Burga H , B (1956) *El Comercio (Lima)*, April 21
136 Burga H , B (1956) *Rev peru Salud publ*, p 341
137 Greenwald, I & Lastres, J B (1953) *Bull Hist Med*, 27, 483
138 Lastres, J B (1954) *Rev Sanid milit Perú*, 27, 5
139 Lastres, J B (1955) *Rev méd Hosp Obrero*, 4, 187
140 Lastres, J B (1958) *Arch ib-amer Hist Med*, 10, 217
141 Monge, C (1921) *Crón. med Peru*, 38, 3
142 Muñoz Puglisevich, J et al (1956) *Arch Pediat Urug*, 27, 200
143 Salazar N , S T (1952) *Bocio endemico en el Peru*, Lima, pp 1-143
144 Salazar N , S T (1953) *Rev Fac Farm Bioquim S Marcos*, 14, 79

Bolivia

145 Balcazar, J M (1946) *Epidemiología Boliviana · La realidad sanitaria en Bolivia*, La Paz, pp 231-235
146 Fernández M , E (1945) *Pren méd argent*, 32, 151
147 Ibáñez B , A (1942) *Bol Ofic sanit panamer.*, 21, 25

Chile

148 Aldunate, G (1959) *Rev méd Chile*, 87, 721
149 Alvarez A, J (1930) *Med mod, Valparaiso*, 4, 697
150 Cabello R, J & Zúñiga C, J (1935) *Rev Med Aliment*, 2, 42
151 Cid Krebs, M (1956) *Estudio del contenido de yodo en los suelos y aguas de la Provincia de Santiago y su relación con el bocio endemico*, Santiago (Thesis, University of Chile)
152 Covarrubias P, A (1943) *Rev. méd Chile*, 71, 713
153 Donoso, F (1959) *Rev méd Chile*, 87, 734
154 Donoso, F et al (1955) *Rev méd Chile*, 83, 246
155 Donoso, F et al (1955) *Rev méd Chile*, Suppl No 6
156 Donoso, F et al (1958) *Rev méd Chile*, 86, 744
157 Donoso, F et al (1959) *Rev méd Chile*, 87, 716
158 Feferholtz, J & Ortiz, A (1951) *Rev méd Chile*, 79, 22
159 Gilliss, J M (1855) *Chile its geography, climate, earthquakes, government, social condition, mineral and agricultural resources, commerce, etc* In *The U S Naval Astronomical Expedition to the Southern Hemisphere, during the years 1849-'50-'51-'52*, Washington, vol. 1, pp 197, 206, 373
160 Greenwald, I (1954) *J clin Endocr*, 14, 800
161 Oberhauser Bund, F & Cid Krebs, M (1958) *Rev cient*, 3, No 7, p 22
162 Romero, H (1943) *Rev chil Hig*, 5, 423
163 Schmidtmeyer, P (1824) *Travels into Chile, over the Andes, in the years 1820 and 1821, with some sketches of the productions and agriculture, mines and metallurgy, inhabitants, history, and other features, of America, particularly of Chile, and Arauco*, London, p 191
164 [illegible] *[illegible]ches of a journey* [illegible]
165 [illegible]
166 Zuñiga C, J (1935) *Un distrito bocigeno*, Santiago (Thesis, University of Chile)

Argentina

167 Alonso M, J C (1939) *Bol sanit Dep nac Hig (B Aires)*, 3, 63
168 Bustos, F M (1949) *Bol Acad argent Cirug.*, 33, 899
169 De La Barrera, J M (1930-32) *Arch Soc Biol Montevideo*, Suppl, p 410
170 De Salas, S M & Amato, F D (1946) *Rev Admin nac Agua (B Aires)*, 10, 101
171 Instituto de Investigaciones Tecnicas (1946-47) *Arch Secret Salud públ*, 1, 56
172 Lewis, J T (1924) *Sem méd (B Aires)*, 2, 713
173 Lobo, M M et al (1938) *Bol sanit Dep nac Hig (B Aires)*, 2, 673
174. Maccarini, H (1951) *Bocio endémico y otras tiropatias en la infancia*, Buenos Aires (Thesis)
175 Maccarini, H. (1951) *Pren méd argent*, 38, 441
176 Maccarini, H. (1956) *Pren méd argent*, 43, 2805
177. Mazzocco, P. (1929) *Rev Soc argent Biol*, 5, 440, 463, 486
178. Mazzocco, P & Arias Aranda, C (1929) *Rev Soc argent Biol*, 5, 472
179. Olascoaga, M L (1957) *Rev Sanid milit argent*, 56, 239
180 Oñativia, A. I (1959) *Med panamer*, 12, 107
181 Pasqualini, R Q (1946) *Rev Asoc méd argent*, 60, 1010
182. Pasqualini, R Q (1946) *Rev Sanid milit (B Aires)*, 45, 1049
183 Perinetti, H (1945) *Bol. Soc. méd Mendoza*, 1, No 11, p 49
184 Perinetti, H (1955) *Dia med*, 27, 75
185. Perinetti, H (1958) *Arch. Sci med*, 105, 179
186 Perinetti, H et al (1952) *Rev Fac Cienc. méd Univ Cuyo*, 1, 7
187 Romero, J H (1952) *Rev Asoc. méd argent*, 66, 193

188 Schiavone, E L (1957) *Rev Sanid milit argent*, 56, 261
189 Schmidtmeyer, P (1824) *Travels into Chile, over the Andes, in the years 1820 and 1821, with some sketches of the productions and agriculture, mines and metallurgy, inhabitants, history, and other features, of America, particularly of Chile, and Arauco*, London, pp 188-194
190 Sordelli, E M (1937) *Bol sanit Dep nac Hig (B Aires)*, 1, 810
191 Stanbury, J B (1953) *Bull Wld Hlth Org*, 9, 183
192 Stanbury, J B et al (1952) *J clin Endocr*, 12, 191
193 Stanbury, J B et al (1954) *Endemic goiter The adaptation of man to iodine deficiency*, Cambridge, Mass

Paraguay

194 Burton, R F (1870) *Letters from the battle-fields of Paraguay*, London, p 11
195 Isasi Fleitas, D (1954) *Indices de bocio endemico en niños escolares de ambos sexos*, Asunción, Paraguay
196 Maas, L C (1946) *An Fac Cienc méd Univ Paraguay*, 6, No 23, p 137
197. Peña, R & Isasi Fleitas, D (1946) *Bol Ofic sanit panamer*, 25, 1090
198. Plunkett, R J (1945) *An Fac Cienc med Univ Paraguay*, 5, No 21, p 33

Uruguay

199 Bauzá, J A (1951) *Arch franç Pédiat*, 8, 72
200 Bauzá, J A, Cerviño, J M & Salveraglio, F J (1955) *Dia med urug*, 22, 454
201 Bauzá, J A, Cerviño, J M & Salveraglio, F (1958) *Arch urug Med*, 51, 402
202 Carlos Negro, R & Gentile Ramos, I (1957) *Arch Pediat Urug*, 28, 633
203 Perez Fontana, V, Bennati, D & Volonterio, M (1935) *El bocio en el Uruguay*, Montevideo (*Publicaciones del Departamento Cientifico de Salud Publica*, Series 2, No 16)
204 Proto, A (1943) *Arch urug Med*, 23, 102

Brazil

205 Arruda Sampaio, A (1940) *Pediat prat (S Paulo)*, 11, 215
206 Arruda Sampaio, A (1941) *Rev paul Med*, 19, 1
207 Arruda Sampaio, A (1942) *Rev paul Med*, 21, 321
208 Arruda Sampaio, A (1943) *An paul Med Cir*, 45, 65
209 Arruda Sampaio, A (1947) *Rev paul Med*, 30, 31
210 Barca Pellon, A et al (1955) *Arch brasil Nutr*, 11, No 2, p 9
211 Barca Pellon, A et al (1956) *Áreas bocígenas do Brasil* (Relatório apresentado pela Divisão de Organização Sanitária ao Sr Diretor Geral do Departamento Nacional de Saude, Rio de Janeiro)
212 Boabaid, S (1957) *Rev brasil Med*, 14, 343
213 Borba Côrtes, A (1949) *Alguns aspectos do bócio endêmico*, Paraná (Thesis)
214 Couto Filho, M (1952) *Campanha nacional contra o bocio endêmico*, Rio de Janeiro
215 De Azevedo Villela, E (1953) *Rev brasil Med*, 10, 196
216 De Melo e Albuquerque, A (1944) *Arch Hig Saude publ*, 9, 107
217 De Paula, A (1949) *Hospital (Rio de J)*, 36, 121
218 Duarte Nunes, A (1938) *Rev Med Hig milit (Rio de J)*, 27, 260
219 Furtado Portugal, H (1947) *Rev Ensino*, 15, 131
220 Lobo Leite, A (1939) *Brasil-méd*, 53, 1031
221 Lobo Leite, A (1942) *Hospital (Rio de J)*, 21, 817
222 Lobo Leite, A (1943) *Mem Inst Osw Cruz*, 38, 1
223 Lobo Leite, A (1944) *Arch brasil Nutr*, 1, 87
224 Lopes, D M (1958) *Hospital (Rio de J)*, 53, 505
225 Lowenstein, F W (1959) *Amer J clin Nutr*, 7, 331, 339
226 Lyra, A & De Melo e Albuquerque, A (1943) *Arch Hig Saude publ*, 8, 59

227 Paes de Oliveira, P. et al. (1955) *Arch. brasil. Med.*, 45, 371
228 Paes de Oliveira, P. et al. (1955) *Hospital (Rio de J.)*, 47, 289
229 Peregrino, J. (1944) *J. Amer. med. Ass.*, 126, 186
230 Pinotti, M. (1958) *Arch. brasil. Med. nav.*, 19, 7223
231 Pinto Viegas, A. (1946) *Brasil-méd.*, 60, 359
232 Silva, W. & Borges, P. (1952) *Trab. Inst. Nutr. Univ. Brasil*, 5, 19

Iceland

233 Sigurjónsson, J. (1938) *Virchows Arch. path. Anat.*, 301, 91
234 Sigurjónsson, J. (1940) *Studies on the human thyroid in Iceland*, Reykjavik
235 Sigurjónsson, J. (1950) *Amer. J. Path.*, 26, 1103

Finland

236 Adlercreutz, E. (1928) *Acta med. scand.*, 69, 1, 187, 325
237 Aldercreutz, E. (1928) *Orientierende Untersuchung über die Verbreitung des Kropfes in Finnland und über deren Zusammenhang mit dem Jodvorkommen im Wasser*, Stockholm
238 Haaranen, S. (1959) *Thyroid weight of pigs in endemic goiter and coastal areas in Finland*. In *Comunicaciónes, XVI Congreso Mundial de Veterinaria, Madrid, 21-27 mayo 1959*, Madrid, vol. 2, p. 81
239 Hiilesmaa, V. (1948) *Studies of the thyroid gland of parturients and newborn infants in southern Finland (Helsinki)*, Helsinki
240 Hiilesmaa, V. (1949) *Ann. Chir. Gynaec. Fenn.*, 38, 104
241 Hiilesmaa, V. (1954) *Duodecim (Helsinki)*, 70, 99
242 Järvinen, K. A. J. & Leikola, E. (1955) *Ann. Med. intern. Fenn.*, 44, 31
243. Järvinen, K. A. J. & Leikola, E. (1956) *Ann. Med. intern. Fenn.*, 45, 1
244 Jussila, R. (1957) *Nord. Med.*, 57, 807
245 Lamberg, B.-A. (1957) *Nord. Med.*, 57, 812
246. Lamberg, B.-A., Wahlberg, P. & Kuhlback, B. (1956) *Nord. Med.*, 55, 354
247 Lamberg, B.-A. et al. (1957) *Acta med. scand.*, 158, 63
248 Lamberg, B.-A. et al. (1958) *J. clin. Endocr.*, 18, 991
249. Peltola, P. & Vartiainen, A. (1954) *Ann. Med. intern. Fenn.*, 43, 209
250. Roine, P. et al. (1958) *Lancet*, 2, 173
251 Saxen, E. A. & Saxén, L. O. (1954) *Docum. Med. geogr. trop. (Amst.)*, 6, 335
252. Setala, A. (1954) *Duodecim (Helsinki)*, 70, 177
253 Uotila, U., Raekallio, J. & Ehrnrooth, W. (1958) *Lancet*, 2, 171
254. Virkki, P. (1956) *Ann. Acad. Sci. Fenn.*, Series A, II. Chemica, No. 71
255. Virtanen, A. I. & Virtanen, E. (1940) *Acta med. scand.*, 105, 268
256 Wahlberg, J. (1938) *Acta med. scand.*, Suppl. No. 94
257 Wahlberg, J. (1938) In *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, p. 71
258 Wahlberg, J. (1939) *Nord. Med.*, 4, 3045
259. Wahlberg, J., Uotila, U. & Turpeinen, O. (1948) *Nord. Med.*, 39, 1692
260 Wahlberg, P. et al. (1957) *Acta med. scand.*, 158, 55

Sweden

261. Greenwald, I. (1956) *J. clin. Endocr.*, 16, 977
262. [illegible]
263 [illegible]
264 [illegible] *Soc. Med. Suecan.)*, 57, 1
265. [illegible]
266 [illegible]
267 [illegible]
268. [illegible]
269. [illegible]

Norway

270

271 91, 1190

272.

273.

274

275. *Kropfprophylaxe mit Meerfischen* In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 532

276 Lunde, G (1928) *Wien klin Wschr*, 41, 15

277. Lunde, G. (1935) *Ein Inland-Kropfgebiet ohne Jodmangel.* In, *Verhandlungsbericht, Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, Bern, p 585

278 Nicolaysen, J (1928) *Aetiologie und Prophylaxe des Kropfes in Norwegen* In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 529

279. Nicolaysen, J (1928) *T norske Lægeforen*, 48, 49

280 Norman, N (1955) *Acta med scand*, 151, 185

281 Skaar, T (1926) *Norsk Mag Lægevid*, 87, 863

Denmark

282

283

284

285 Iversen, K (1948) *Temporary rise in the frequency of thyrotoxicosis in Denmark 1941-1945*, Copenhagen

286 Iversen, K (1949) *Amer J med Sci*, 217, 121

287 Meulengracht, E (1945) *Acta med scand*, 121, 446

288 Rosenquist, K (1943) *Om strumaproblemet paa grundlag af en undersogelse i tre Danske landsogne (The goitre problem elucidated through studies in three rural districts in Denmark)*, København

Estonian SSR, Latvian SSR and Lithuanian SSR

289 Ilinskii, S P (1956) *Latv PSR Zinät Akad Vēst*, No 3, p 103

290 Ilinskii, S P (1957) *Latv PSR Zinät Akad Vēst*, No. 9, p. 99

291 Ilinskii, S P (1958) *Latv PSR Zinät Akad Vēst*, No 9, p 63

292 Justus, B (1913) *Beitrage zu dem Vorkommen und der geographischen Verbreitung des Kropfes in der Provinz Ostpreussen*, Konigsberg (Thesis)

293 Kupzis, J (1930) *Latv Augstskol [Univ] Raksti*, 1, 425

294 Kupzis, J (1932) *Z Hyg. InfektKr*, 113, 551

295 Lewin, F (1928) *Statistische Erhebungen uber die Verbreitung des Kropfes in Ostpreussen*, Konigsberg (Thesis)

296 McClendon, J F (1939) *Iodine and the incidence of goiter*, Minneapolis, p 72

297 Ucke, A (1933) *Beitr path Anat*, 92, 253

Netherlands

298 Binnerts, W T (1954) *Nature (Lond)*, 174, 973

299 Binnerts, W T (1956) *Het joduumgehalte van melk*, Amsterdam (Thesis)

300 Brand, B (1917) *Vergrooting der schildklier in Nederland Rapport van den centralen gezondheidsraad*, Utrecht, p 15

301 De Josselin de Jong, R (1952) *Docum Med geogr trop (Amst)*, 4, 370

302 Gezondheidsorganisatie T N O (1959) *De endemische krop in Nederland*, Assen

303 Hipsley, E H (1956) *Med J Aust*, 1, 532

304 Josephus Jitta, N M et al (1932) *Het kropvraagstuk in Nederland Uitgegeven door den voorzitter van den gezondheidsraad*, 's Gravenhage

227 Paes de Oliveira, P et al. (1955) *Arch brasil. Med*, 45, 371
228 Paes de Oliveira, P et al (1955) *Hospital (Rio de J.)*, 47, 289
229. Peregrino, J (1944) *J Amer med Ass*, 126, 186
230. Pinotti, M (1958) *Arch brasil Med nav*, 19, 7223
231 Pinto Viegas, A. (1946) *Brasil-méd*, 60, 359
232 Silva, W & Borges, P (1952) *Trab. Inst Nutr. Univ. Brasil*, 5, 19

Iceland

233 Sigurjónsson, J. (1938) *Virchows Arch. path Anat*, 301, 91
234. Sigurjónsson, J (1940) *Studies on the human thyroid in Iceland*, Reykjavik
235 Sigurjónsson, J (1950) *Amer. J Path*, 26, 1103

Finland

236 Adlercreutz, E (1928) *Acta med. scand*, 69, 1, 187, 325
237 Aldercreutz, E (1928) *Orientierende Untersuchung uber die Verbreitung des Kropfes in Finnland und uber deren Zusammenhang mit dem Jodvorkommen im Wasser*, Stockholm
238 Haaranen, S (1959) *Thyroid weight of pigs in endemic goiter and coastal areas in Finland* In *Comunicaciónes, XVI Congreso Mundial de Veterinaria, Madrid, 21-27 mayo 1959*, Madrid, vol. 2, p 81
239 Hiilesmaa, V. (1948) *Studies of the thyroid gland of parturients and newborn infants in southern Finland (Helsinki)*, Helsinki
240 Hiilesmaa, V (1949) *Ann Chir. Gynaec Fenn.*, 38, 104
241 Hiilesmaa, V. (1954) *Duodecim (Helsinki)*, 70, 99
242. Jarvinen, K A. J. & Leikola, E (1955) *Ann Med intern Fenn*, 44, 31
243 Jarvinen, K A J & Leikola, E (1956) *Ann Med intern Fenn*, 45, 1
244 Jussila, R (1957) *Nord Med*, 57, 807
245 Lamberg, B-A (1957) *Nord Med*, 57, 812
246 Lamberg, B-A, Wahlberg, P. & Kuhlback, B (1956) *Nord Med*, 55, 354
247 Lamberg, B-A et al (1957) *Acta med scand*, 158, 63
248 Lamberg, B-A et al (1958) *J clin Endocr*, 18, 991
249. Peltola, P & Vartiainen, A (1954) *Ann Med intern Fenn*, 43, 209
250 Roine, P. et al (1958) *Lancet*, 2, 173
251 Saxén, E A & Saxen, L O (1954) *Docum Med geogr trop (Amst)*, 6, 335
252 Setala, A (1954) *Duodecim (Helsinki)*, 70, 177
253. Uotila, U, Raekallio, J & Ehrnrooth, W (1958) *Lancet*, 2, 171
254. Vilkki, P (1956) *Ann Acad Sci Fenn*, Series A, II Chemica, No 71
255 Virtanen, A I & Virtanen, E (1940) *Acta med scand*, 105, 268
256 Wahlberg, J (1938) *Acta med scand*, Suppl No 94
257. Wahlberg, J (1938) In *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, p 71
258 Wahlberg, J (1939) *Nord Med*, 4, 3045
259 Wahlberg, J, Uotila, U. & Turpeinen, O (1948) *Nord Med*, 39, 1692
260. Wahlberg, P et al (1957) *Acta med scand*, 158, 55

Sweden

261 Greenwald, I (1956) *J clin Endocr.*, 16, 977
262. Hojer, J A (1931) *Hygeia (Stockh)*, 93, 577
263. [illegible]
264. [illegible] *Soc. Med Suecan*, 57, 1
265 [illegible]
266. [illegible]
267. [illegible]
268 [illegible]
269. [illegible]

Norway

270. Devold, O & Closs, K. (1941) *Nord Med*, **10**, 1694
271. Iversen, T., Lunde, G & Wülfert, K. (1930) *Norsk Mag Lægevid*, **91**, 1190
272. Johannessen, A. (1891) *Z. klin Med*, **19**, 194
273. Kjølstad, S. (1921) *Norsk Mag Lægevid*, **82**, 729
274 Lunde, G (1928) *Northw Med (Seattle)*, **27**, 412, 479
275 Lunde, G (1928) *Über die Jodausscheidung durch den Harn und über Kropfprophylaxe mit Meerfischen* In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 532
276 Lunde, G (1928) *Wien klin Wschr*, **41**, 15
277 Lunde, G (1935) *Ein Inland-Kropfgebiet ohne Jodmangel* In *Verhandlungsbericht, Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, Bern, p 585
278 Nicolaysen, J (1928) *Aetiologie und Prophylaxe des Kropfes in Norwegen* In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 529
279 Nicolaysen, J. (1928) *T norske Lægeforen*, **48**, 49
280 Norman, N (1955) *Acta med scand*, **151**, 185
281 Skaar, T (1926) *Norsk Mag Lægevid*, **87**, 863

Denmark

282 Bastenie, P. A (1947) *Lancet*, **1**, 789
283. Dalsgaard-Nielsen, T (1933) *Ugeskr Læg*, **95**, 1067
284 Dalsgaard-Nielsen, T (1940) *Ugeskr Læg*, **102**, 845
285 Iversen, K (1948) *Temporary rise in the frequency of thyrotoxicosis in Denmark 1941-1945*, Copenhagen
286 Iversen, K. (1949) *Amer J med Sci*, **217**, 121
287 Meulengracht, E (1945) *Acta med scand*, **121**, 446
288 Rosenquist, K (1943) *Om strumaproblemet paa grundlag af en undersøgelse i tre Danske landsogne (The goitre problem elucidated through studies in three rural districts in Denmark)*, København

Estonian SSR, Latvian SSR and Lithuanian SSR

289 Ilinskii, S P (1956) *Latv PSR Zinãt Akad Vēst*, No 3, p 103
290 Ilinskii, S P (1957) *Latv PSR Zinãt Akad Vēst*, No 9, p 99
291 Ilinskii, S P (1958) *Latv PSR Zinãt Akad Vēst*, No 9, p 63
292 Justus, B (1913) *Beiträge zu dem Vorkommen und der geographischen Verbreitung des Kropfes in der Provinz Ostpreussen*, Königsberg (Thesis)
293 Kupzis, J (1930) *Latv Augstskol [Univ] Raksti*, **1**, 425
294 Kupzis, J (1932) *Z Hyg InfektKr*, **113**, 551
295. Lewin, F (1928) *Statistische Erhebungen über die Verbreitung des Kropfes in Ostpreussen*, Königsberg (Thesis)
296 McClendon, J F (1939) *Iodine and the incidence of goiter*, Minneapolis, p 72
297 Ucke, A (1933) *Beitr path Anat*, **92**, 253

Netherlands

298 Binnerts, W T (1954) *Nature (Lond)*, **174**, 973
299 Binnerts, W T (1956) *Het joduumgehalte van melk*, Amsterdam (Thesis)
300 Brand, B (1917) *Vergrooting der schildklier in Nederland Rapport van den centralen gezondheidsraad*, Utrecht, p 15
301 De Josselin de Jong, R (1952) *Docum Med geogr trop (Amst)*, **4**, 370
302 Gezondheidsorganisatie T N O (1959) *De endemische krop in Nederland*, Assen
303 Hipsley, E H (1956) *Med J Aust*, **1**, 532
304 Josephus Jitta, N M et al (1932) *Het kropvraagstuk in Nederland Uitgegeven door den voorzitter van den gezondheidsraad*, 's Gravenhage

227 Paes de Oliveira, P et al (1955) *Arch brasil. Med*, 45, 371
228. Paes de Oliveira, P. et al (1955) *Hospital (Rio de J.)*, 47, 289
229. Peregrino, J. (1944) *J Amer med Ass*, 126, 186
230 Pinotti, M (1958) *Arch brasil. Med. nav*, 19, 7223
231 Pinto Viegas, A (1946) *Brasil-méd*, 60, 359
232 Silva, W. & Borges, P (1952) *Trab Inst. Nutr. Univ Brasil*, 5, 19

Iceland

233 Sigurjónsson, J (1938) *Virchows Arch path Anat*, 301, 91
234 Sigurjónsson, J (1940) *Studies on the human thyroid in Iceland*, Reykjavik
235 Sigurjónsson, J (1950) *Amer J Path.*, 26, 1103

Finland

236 Adlercreutz, E (1928) *Acta med scand*, 69, 1, 187, 325
237 Aldercreutz, E (1928) *Orientierende Untersuchung uber die Verbreitung des Kropfes in Finnland und uber deren Zusammenhang mit dem Jodvorkommen im Wasser*, Stockholm
238 Haaranen, S (1959) *Thyroid weight of pigs in endemic goiter and coastal areas in Finland* In *Comunicaciónes, XVI Congreso Mundial de Veterinaria, Madrid, 21-27 mayo 1959*, Madrid, vol 2, p 81
239 Hiilesmaa, V. (1948) *Studies of the thyroid gland of parturients and newborn infants in southern Finland (Helsinki)*, Helsinki
240 Hiilesmaa, V (1949) *Ann Chir Gynaec Fenn*, 38, 104
241 Hiilesmaa, V (1954) *Duodecim (Helsinki)*, 70, 99
242. Jarvinen, K A J & Leikola, E (1955) *Ann Med intern Fenn*, 44, 31
243 Jarvinen, K A J & Leikola, E (1956) *Ann Med. intern Fenn*, 45, 1
244 Jussila, R (1957) *Nord. Med*, 57, 807
245 Lamberg, B-A. (1957) *Nord Med*, 57, 812
246 [illegible] (1956) *Nord Med*, 55, 354
247 [illegible]
248. [illegible]
249. [illegible]
250. [illegible]
251 [illegible] *cum Med geogr trop (Amst)*, 6, 335
252. [illegible] 70, 177
253 Uotila, U, Raekallio, J & Ehrnrooth, W (1958) *Lancet*, 2, 171
254. Vilkki, P (1956) *Ann Acad Sci Fenn*, Series A, II. Chemica, No 71
255 Virtanen, A I & Virtanen, E. (1940) *Acta med scand*, 105, 268
256 Wahlberg, J (1938) *Acta med scand*, Suppl No 94
257 Wahlberg, J (1938) In: *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, p 71
258 Wahlberg, J (1939) *Nord Med*, 4, 3045
259 Wahlberg, J., Uotila, U & Turpeinen, O (1948) *Nord Med*, 39, 1692
260. Wahlberg, P et al (1957) *Acta med scand*, 158, 55

Sweden

261. Greenwald, I (1956) *J. clin Endocr*, 16, 977
262. [illegible]
263. [illegible]
264. [illegible] *Soc Med Suecan)*, 57, 1
265. [illegible]
266. [illegible]
267 [illegible]
268 [illegible]
269 [illegible]

349. Chukanin, N. N & Levitin, V. Ya (1959) *Probl Endokr. Gormonoter*, 5, No 2, p. 96
350. Davidova, L. M. (1957) *Probl Endokr. Gormonoter.*, 3, No 5, p. 93
351 Efimov, A S (1959) *Probl Endokr. Gormonoter*, 5, No 3, p 113
352. Egorov, K. A & Orudzhiev, I. (1936) *Vop Endokr*, 1, 983
353 Fedinets, A. V (1955) *Probl Endokr Gormonoter.*, 1, No 2, p 39
354 Florinsku, V. A. (1954) *Gig. i Sanit.*, No. 4, p 44
355 Florinsku, V A. (1959) *Probl Endokr Gormonoter.*, 5, No 6, p 93
356 Gelovani, G A. (1928) In· *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, p 98
357. Goncharov, A T. (1957) *Sborn. nauch. Rab*, *Kazan Gos med Inst*, No. 1, p 97
358 Gurevich, G P (1958) *Probl. Endokr Gormonoter*, 4, No. 1, p. 100
359. Gurevich, G. P. (1958) *Probl Endokr Gormonoter*, 4, No 5, p 106
360 Gurevich, G P & Mukhina, L. D. (1958) *Probl Endokr Gormonoter*, 4, No. 6, p. 52
361 Ionisyants, V. P. (1959) *Probl Endokr. Gormonoter.*, 5, No 3, p 91
362. Ionisyants, V P (1959) *Probl Endokr Gormonoter*, 5, No 6, p 98
363 Isakova, E. N. (1956) *Probl. Endokr Gormonoter*, 2, No 3, p 22
364 Kalishevskaya, V I (1956) *Probl Endokr Gormonoter*, 2, No 2, p 56
365. Kamchatnov, V P (1953) *Gig i Sanit*, No 2, p 33
366 Kamchatnov, V P (1957) *Sborn nauch. Rab.*, *Kazan Gos. med Inst*, No 1, p 47
367 Kamchatnov, V P (1959) *Gig i Sanit*, No 4, p 76
368 Karpova, E. V. (1955) *Probl Endokr Gormonoter*, 1, No. 5, p 68
369. Karpova, E V. (1957) *Probl Endokr Gormonoter*, 3, No 3, p 75
370 Kharitonova, V. A (1957) *Probl Endokr. Gormonoter*, 3, No 3, p. 83
371. Kharitonova, V. A (1959) *Probl Endokr Gormonoter*, 5, No. 5, p 85
372 Khazan, V. B (1949) *Gig i Sanit*, No 6, p 41
373 Khvorov, V V (1959) *Probl Endokr Gormonoter*, 5, No 1, p 80
374 Khvorov, V V. & Ionisyants, V. P (1959) *Probl Endokr. Gormonoter*, 5, No. 2, p 98
375 Kolomutseva, M G. (1949) *Gig i Sanit*, No 6, p. 43
376 Korabel'nikov, I D. (1956) *Probl Endokr Gormonoter*, 2, No 4, p. 120
377 Koval'sku, V V (1958) *Vestn Sel'skohozjaj Nauk*, 3, No 9, p 50
378 Kruchinina, I P (1958) *Izv Akad. Nauk Uzbek S S R*, *Ser med*, No 1, p. 29
379 Kutsherenko, P O (1936) *Radjanska Med*, No 3, p. 25
380 Kutsherenko, P O (1936) In *Symposium to celebrate 35th anniversary of scientific work of A I Abrikosov*, Moscow-Leningrad, p 127
381 Kutsherenko, P O, Judina, N & Kutsherenko, B P (1934) *Ž med. Cik. (Kiev)*, 4, 163
382 Kutsherenko, P O, Judina, N. & Rimak, F (1933) *Ž med Cik (Kiev)*, 3, 79
383 Kuznetsov, V N (1936) *Trud Kubansk med Inst*, 3, 143
384 Landishev, Yu. S (1959) *Probl Endokr Gormonoter*, 5, No 4, p 99
385 Lyapustin, V A (1936) *Vop Endokr*, 1, 976
386 Mamedov, Z (1936) *Azerbaidzhan. med Ž*, 1, No 43, p 34
387 Mamedov, Z M & Orudzhiev, I. M. (1959) *Probl. Endokr Gormonoter*, 5, No. 2, p 84
388 Marco Polo (1275) *Travels of Marco Polo the Venetian*, London, J M Dent & Sons, 1908, p. 95
389 Masumov, S A. (1936) *Bull Uzbekist Inst exp Med*, No 4, p 34
390 Mayer, C F (1959) *Milit Med*, 124, 607
391 Melnic, I A (1957) *Probl Endokr Gormonoter*, 3, No 1, p 108
392 Merkeshina, L G (1958) *Vrač Delo*, p 1189
393 Meshchenko, V. M (1957) *Probl Endokr Gormonoter*, 3, No 2, p 108
394 Meshchenko, V. M (1957) *Vrač. Delo*, p 739
395 Mikhailov, Yu. M. (1959) *Probl Endokr. Gormonoter*, 5, No 4, p 102
396 Mirochnik, F. M (1955) *Probl. Endokr. Gormonoter*, 1, No 5, p 19
397 Nazaryev, A. I (1959) *Probl. Endokr. Gormonoter*, 5, No 4, p. 97

305 Kaayk, C K J (1955) *Voeding en voedingstoestand van het schoolkind ten plattelande*, Leiden (Thesis)
306 Pasma, F (1947) *De endemische krop em haar gevolgen in den z o. hoek van Friesland*, Wolvega
307 Pasma, F (1951) *T N O -Nieuws*, **6**, 143
308 Pasma, F (1955) *T N O -Nieuws*, **10**, 429
309 Reith, J F (1933) *Schweiz med Wschr*, **63**, 791
310 Terpstra, J (1956) *De schildklierfunctie bij endemische krop*, Leiden (Thesis)
311 Terpstra, J & Querido, A (1959) *Acta endocr (Kbh)*, **31**, 433

Poland

312 Chilean Iodine Educational Bureau (1956) *Geochemistry of iodine*, London
313 Chodzko, W & Tubiasz, S (1934) *Med dośw spol*, **18**, 410
314 Ciechanowski, S (1934) *Virchows Arch path Anat*, **293**, 97
315 Czyzewski, K & Falkiewicz, A (1952) *Pol Tyg lek*, **7**, 1106
316 Czyzewski, K et al (1953) *Pol Tyg lek*, **8**, 1735
317 Czyzewski, K et al (1954) *Arch Immunol Ter dośw*, **2**, 49
318 Czyzewski, K et al (1956) *Arch Immunol Ter dośw*, **4**, 275
319 Czyzewski, K et al (1958) *Arch Immunol Ter dośw*, **6**, 653
320 Hauke, H (1927) *Mitt Grenzgeb Med Chir*, **40**, 327
321 Heller, J (1938) *Zdrow publ*, **53**, 449
322 Heller, J (1951) *Postępy Hig Med dośw*, **4**, 44
323 Karbowski, J (1957) *Zdrow publ*, No 6, p 517
324 Król, W & Stylo, D (1957) *Pol Tyg lek*, **12**, 2019
325 Liek, E (1925) *Dtsch med Wschr*, **51**, 1779
326 Liek, E (1927) *Münch med Wschr*, **74**, 1786
327 Liek, E (1928) *Arztl Rundsch*, **38**, 365, 382
328 Liek, E (1928) *Z wiss Bäderk*, **3**, 207
329 Liek, E (1929) *Arztl Rundsch*, **39**, 4
330 Nowakowski, B (1947) *Pol Tyg lek*, **2**, 1152, 1180
331 Samelson, S (1933) *Mschr Kinderheilk*, **58**, 48
332 Tubiasz, S (1933) *Bull Off int Hyg publ*, **25**, 466
333 Tubiasz, S (1938) In *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, p 91
334 Tubiasz, S (1940) *Bull Off int. Hyg publ*, **32**, 667

USSR (excluding Estonian SSR, Latvian SSR and Lithuanian SSR)

335 Abdulakhatov, A M (1958) *Izv Akad Nauk Uzbek S S R, Ser med*, No 1, p 33
336 Aber, V Ya (1958) *Probl Endokr Gormonoter*, **4**, No 2, p 47
337 Alfeev, N A (1936) *Trud Kubansk med Inst*, **3**, 186
338. Alikishibekov, M M (1959) *Probl Endokr Gormonoter*, **5**, No 2, p 91
339 Antonov, Yu G (1959) *Izv Akad Nauk S S S R, Ser biol*, No 2, p 193
340 Arndt, H J (1931) *Der Kropf in Russland*, Jena, Fischer
341 Aslanishvili, I A (1945) *Vrač Delo*, **25**, 359
342. Balakhovskaya, M I & Ionisyants, V P (1958) *Probl Endokr Gormonoter*, **4**, No 2, p. 92
343 Balakhovskaya, M I & Liubskaya, I I (1957) *Probl Endokr. Gormonoter*, **3**, No 1, p 80
344 Belikhova, E L (1955) *Probl Endokr Gormonoter*, **1**, No 5, p 28
345 Bergman, S I (1957) *Probl Endokr Gormonoter*, **3**, No 2, p 74
346 Bolotova, T P. (1955) *Probl Endokr Gormonoter.*, **1**, No 5, p 36
347. Chekalov, F. I (1936) *Vop Endokr*, **1**, 987
348 Cherkinski, S. N & Zaslavskaya, R M (1956) *Probl Endokr. Gormonoter*, **2**, No 4, p 70

445 Milcu, S M et al (1953) *Stud Cercet. Endocr*, 4, 186
446. Milcu, S M. et al (1953) *Stud. Cercet. Endocr*, 4, 199
447. Negoescu, I (1953) *Stud Cercet Endocr*, 4, 221
448 Straus, K. (1956) *Tr. Leningr. sanit.-gig med Inst*, 26, 146

Bulgaria

449 Gorchakov, A K (1958) *Suvr. Med*, 9, No 5, p 3
450. Grigorov, L et al (1958) *Nauch Tr nauch izsled sanit khig Inst (Sofija), 1957*, p. 3
451. Kafedzhieva, L (1959) *Nauch Tr izsled sanit khig Inst (Sofija), 1958*, p 240
452 Khaidudov, L, Chervenivanov, G. & Armenkov, A (1956) *Sborn Tr vissh. med Inst I P Pavlov (Plovdiv), 1953-1954*, 8, 279
453 Khranova, A (1953) *Izv med Inst (Sofija)*, 8, 115
454 Khristov, I (1957) *Nauch Tr nauch izsled sanit. khig Inst (Sofija), 1954-1956*, p. 37
455. Penchev, I, Vurbanov, V & Dishliev, D (1957) *Nauch Tr. Inst Spetsial. Usuv Lek (Sofija), 1955*, 4, No 1, p 25
456 Penchev, I et al (1957) *Nauch Tr. Inst Spetsial Usuv Lek (Sofija), 1955*, 4, No 1, p. 3
457. Penchev, I et al (1957) *Nauch Tr Inst Spetsial Usuv Lek (Sofija), 1955*, 4, No 1, p 47
458 Penchev, I et al (1957) *Nauch Tr. Inst Spetsial Usuv Lek. (Sofija), 1955*, 4, No 1, p 61
459 Penchev, I et al (1958) *Suvr Med*, 9, No 8, p 3
460 Staikov, T T (1956) *Sred med Rab*, No 4, p 13
461 Ticholov, K. (1947) *Med Let*, 39, 978
462 Tsvetkov, L (1956) *Nauch Tr vissh med Inst Vulko Chervenkov (Sofija), 1954*, 2, No 4, p 71
463 Vasilev, T & Dimitrov, N (1956) *Suvr Med*, 7, No 6, p 24
464 Vurbanov, V & Dishliev, D (1957) *Endemichna gusha*, Sofia

Yugoslavia

465 Arko, V (1953) *Higijena*, 5, 219
466 Brožek, J & Ferber, E (1955) *Nutr Rev*, 13, 97
467. Buzina, R et al (1955) *Higijena*, 7, 329
468 Buzina, R et al (1959) *J Nutr*, 68, 465
469 Ceramilac, A (1954) *Vo -sanit Pregl*, 11, 317
470 Ferber, E et al (1955) *Higijena*, 7, 295
471 Gušić, B et al (1957) *Med Zap (Titograd)*, 148 pp
472 Gvozdenović, D M (1957) *Glas Hig Inst. Srbije*, 6, Nos 3-4, p 67
473 Horvat, A & Maver, H (1958) *J Nutr*, 66, 189
474 Horvat, A et al (1959) *J Nutr*, 68, 647
475 Jovanovic, M, Pantić, V & Markovic, B (1953) *Acta vet (Beogr)*, 3, No. 1, p 31
476 Jovanovic, M., Pantic, V & Markovic, B (1956) *Rec Méd vet*, 132, 594
477 Kališnik, M (1956) *Higijena*, 8, 1
478 Kičic, M & Radmili, V (1955) *Vo -sanit Pregl*, 12, 241
479 Lodge, O (1942) *Peasant life in Yugoslavia*, London, p 87
480 Matovinović, J (1953) *Bull Wld Hlth Org*, 9, 249
481 Maver, H & Horvat, A (1959) *Gušavost na otocima Sjevernog Jadrana* In *Prvi Jugoslovenski Simpozijum o Gušavosti, Beograd, 1957*, Beograd, p 103
482 Miholić S (1936) *Bull Soc chim Yougoslavie*, 7, 133
483 Pantic, V & Jovanovic, M (1955) *Acta vet (Beogr)*, 5, No 1, p 13
484 Perovic, S (1955) *Higyera*, 7, 337
485 Petrov, S (1955) *Higijena*, 7, 322
486 Prebeg, Z et al (1955) *Higijena*, 7, 307
487 Radojčic, B & Joksimovic, S (1948) *Vo -sanit Pregl*, 5, 87
488 Ramzin, S (1954) *Bibl Hig Inst Srbije*, No. 5, p 26

398 Nikolaev, O V. (1936) *Vop Endokr*, 1, 175

399 Nikolaev, O V (1955) *Probl Endokr Gormonoter*, 1, No 5, p 4

400 Nikolaev, O V (1957) *Probl Endokr Gormonoter*, 3, No 5, p 57

401 Nizhibitski, N. N (1936) *Trud Kubansk med Inst*, 3, 109

402. Obliiarov, D O (1958) *Izv Akad. Nauk Uzbek S S R*, *Ser med*, No 1, p 23

403. Plotnikova, Yu I (1959) *Probl Endokr. Gormonoter*, 5, No. 3, p 74

404 Primak, F Y (1936) *Med Ž (Kiev)*, 6, No 1, p 165

405. Rodnjanski, B B (1958) *Probl Endokr Gormonoter*, 4, No 3, p. 124

406 Rybalkin, P E (1947) *Klin Med (Mosk)*, 25, No 12, p 80

407 Santotski, M. I & Khvorov, V V (1958) *Probl Endokr Gormonoter*, 4, No 5, p 92

408 Savchenko, P S (1955) *Probl Endokr Gormonoter*., 1, No 1, p 47

409 Savchenko, P S (1956) *Dokl Akad. Nauk S S S.R*, 108, 889

410 Schermann, S. I (1932) *Virchows Arch. path Anat*., 287, 363

411 Shinkerman, N M (1956) *Probl Endokr Gormonoter*., 2, No 4, p 60

412. Shinkerman, N M (1956) *Probl Endokr. Gormonoter*., 2, No. 6, p. 66

413 Shkarenko, Z S (1936) *Social Zdravookh Uzbek*, No 3, p 50

414. Shmagina, M D & Usmanova, G M (1959) *Probl Endokr. Gormonoter*, 5, No 4, p 101

415 Shulpinov, S S (1957) *Sborn nauch Rab*, *Kazan Gos med Inst*, No 1, p 5

416 Shvetz, A S. (1958) *Gig i Sanit*, 23, No 4, p 71

417 Skatkov, M E (1956) *Probl Endokr Gormonoter*, 2, No. 1, p 111

418. Skatkov, M. E. (1956) *Probl. Endokr Gormonoter*, 2, No 3, p 29

419 Skatkov, M E (1957) *Probl Endokr Gormonoter*, 3, No 6, p 90

420. Skatkov, M E. (1959) *Probl Endokr Gormonoter*, 5, No. 2, p 111

421 Slavin, V D (1936) *Vop Endokr*, 1, 262, 365

422 Strunnokov, A N (1936) *Trud Kubansk. med. Inst*, 3, 171

423 Tabakov, N. A (1936) *Vop. Endokr*, 1, 994

424 Tikhonova, E P & Shifman, L M (1958) *Probl. Endokr Gormonoter*, 4, No 2, p 108

425 Tsarikovskaya, N G, Breslavski, A. S & Krizhanovskaya, M V (1958) *Probl Endokr Gormonoter*, 4, No. 5, p 97

426 Udod, V. M. (1958) *Gig i Sanit*, 23, No. 6, p. 63

427. Valedinskaya, L K (1936) *Vop Endokr*, 1, 999

428 Zhukovski, I N (1936) *Trud Kubansk med. Inst*, 3, 119

Romania

429. Andronovici, G (1945) *Bull Acad Méd Roum*, 17, 255

430. Banu, G & Dinu, I (1946) *Bull Acad Méd Roum*, 19, 401

431 Câmpeanu, L (1924) *Problema guşei şi cretinizmului in România*, Cluj

432 Danielopolu, D. (1934) *Bull Off int Hyg publ*, 26, 1601

433. Danielopolu, D. & Nicolaie, D (1936) *Bull Off int Hyg publ*, 28, 288

434 Danielopolu, D et al (1935) *Bull Off. int. Hyg publ*, 27, 706

435 Danielopolu, D et al (1935) *Gaz Hôp. (Paris)*, 108, 1741

436 [illegible] 7, 227; 3, 33

437 [illegible] s

438. [illegible]

439. [illegible] harest, vol 1

440. Milcu, S M (ed) (1958) *Guşa endemică Distrofia endemică tireopată*, Bucharest, vol 2

441. Milcu, S M & Negoescu, I (1957) *Rum med. Rev (Bucharest)*, 1, No 1, p 60

442. [illegible] *Ştiinţifice*, 2-12. *Iunie*, p 1208

443. [illegible]

444. [illegible]

63

536 Várbıró, B , Száva, I & Koch, S. (1953) *Gyermekgyógyászat*, 4, 314
537. Véli, G (1953) *Gyermekgyogyászat*, 4, 311

Czechoslovakia

538 Dolecek, R (1952) *Čas Lék. čes* , 91, 149
539. Feix, Č , Rezler, D & Šilink, K (1949) *Čas. Lék ces* , 88, 845
540 Feix, Č Rezler, D & Šilink, K. (1949) *Čas Lék. ces* , 88, 1482
541. Fleischhans, B (1948) *Čas Lék čes.*, 87, 493
542. Horáčková, M & Pokorný, M. (1951) *Čas. Lék. čes.*, 90, 799
543 Hostomská et al (1954) *Čas Lék čes* , 93, 1064
544 Klima, J (1934) *Čas Lék. čes* , 73, 141
545 Kouba, K (1956) *Čsl Pediat* , 11, 446
546 Langer, P (1956) *Dokl preventiv. Starostliv Endokr* , p 33
547 Langer, P. (1957) *Čsl Gastroent Výž*, 11, 318
548 Langer, P , Sedlák, J & Michajlovskij, N (1958) In: *Problémy Endokrinologickej Praxe z Hl'adiska Výskumu*, Bratislava, p 9
549. Langer, P et al (1958) *Arch Sci med*, 105, 257
550 Németh, Š (1953) *Bratisl lek Listy*, 33, 661
551 Nemeth, Š & Podoba, J (1955) *Bratisl lek. Listy*, 35, 13
552. Nemeth, Š & Štukovsky, R (1958) *Čsl Pediat* , 13, 97
553 Podoba, J (1953) *Bratisl. lek Listy*, 33, 309
554 Podoba, J (1956) *Dokl preventiv Starostliv Endokr* , p 11
555. Podoba, J , Németh, S. & Grmelová, M (1950) *Bratisl lek Listy*, 30, 397
556 Podoba, J et al (1957) *Bratisl lek Listy*, 37, 67
557 Reisenauer, R & Likar, O (1958) *Čsl Hyg* , 3, 355
558 Reisenauer, R , Šilink, K & Rohling, S (1956) *Sborn lék* , 58, 77
559 Reisenauer, R , Šilink, K & Rohling, S (1959) *Čas Lék. čes* , 98, 499
560 Šilink, K & Maršíková, L (1951) *Nature (Lond)*, 167, 528
561 Šilink, K & Reisenauer, R (1957) *Čas Lék čes* , 96, 809
562 Šilink, K , Reisenauer, R & Chaloupsky, J (1959) *Rev Czech Med* , 5, 73
563 Šilink, K et al (1957) *Čas Lék čes* , 96, 1509
564 Slovenská Akademie Věd a Uměni (1951) *Research on goitre in Slovakia some results from the area of Banska Bystrica*, Bratislava
565 Stukovsky, R et al (1960) *Vet Med (Praha)*, 5, No 2, p 129
566 Štukovský, R et al (1960) *Vet Med (Praha)*, 5, No 2, p 143
567 Suk, V (1931) *Anthropologie (Praha)*, 9, No 1, p 1
568 Tománek, E (1935) *Bratisl lek Listy*, 15, Suppl No. 7, p 128
569 Verner, M (1958) In *Problemy Endokrinologickej Praxe z Hl'adiska Výskumu*, Bratislava, p 43
570 Vohnout, C S & Pihar, O (1950) *Čas Lek čes* , 89, 579
571 Vomela, S (1929) *Rev Neurol Psychiat (Praha)*, 26, 81
572 Vomela, S (1932) *Ann Méd*, 32, 461

Germany

573 Albeaux-Fernet et al (1945) *Bull Soc. méd Hop Paris*, 61, 434
574 Aschoff, L (1935) *Arch Kinderheilk* , 105, 159
575 Balks, R (1935) *Landw Jb* , 81, 939
576 Bauer, J (1952) *Med Klin* , 47, 530
577 B[illegible]
578 B[illegible]
579 B[illegible]
580 B[illegible]
581 Breitner, B (1926-27) *Mitt Grenzgeb Med Chir.*, 40, 288
582 Bukatsch, F , Haubold, H. & Lackner, F (1951) *Klin Wschr* , 29, 450
583 Cauer, H (1929) *Z ges phys Ther* , 37, 203

489 Ramzın, S & Alković, G. (1955) *Higijena*, 7, 284
490. 496
491
492 71
493
494. 19, 953

Greece

495 Hadjidakis, S. G (1959) *Acta paediat* (*Uppsala*), 48, 12

Austria

496. Abels, H. (1931) *Krankheitsforschung*, 9, 241
497. Bauhofer, F (1952) *Wien med Wschr.*, 102, 484
498. Baumgartner, W (1939) *Beitr. klin Chir*, 169, 573
499 Burtscher, J & Sprenger, W (1935) *Wien klin. Wschr.*, 48, 1231
500 Davidson, C S et al (1947) *J Lab clin Med*, 32, 1470
501. Kopf, H (1952) *Wien med Wschr*, 102, 502
502. Kopf, H (1954) *Wien klin Wschr*, 66, 96
503 Kostl, F. (1855) *Der endemische Cretinismus als Gegenstand der öffentlichen Fürsorge*, Wien
504. Kriebernig, E (1950) *Wien klin Wschr*, 62, 105
505. *Wien med Wschr*, 104, 777
506
507 *chr*, 99, 396
508.
509
510. 2
511. 797
512. *Kropfverhutung in Österreich*, Berlin & Wien

Hungary

513 Bodnár, J & Straub, J (1930) *Biochem Z.*, 227, 237
514. Daday, A (1959) *Orsz orvostort Konyv Kozl*, No. 12, p. 133
515. Gortvay, G (1925) *Népegészségugy*, 6, 889
516. Hal, J & Horváth, M (1947) *Orv Lapja*, 3, 798
517 Horváth, M. (1951) *Gyermekgyógyászat*, 2, 333
518. Horváth, M., Nógrádi, G & Dános, L. (1949) *Orv. Hetil.*, 90, 360
519.
520.
521.
522.
523
524. Sós, J. (1953) *Gyermekgyógyászat*, 4, 193
525 Sós, J., Fekete, L. & Molnár, M (1947) *Orv Lapja*, 3, 1249
526.
527. 117
528.
529.
530.
531.
532.
533. 2, 72
534.
535.

536 Várbíró, B, Száva, I. & Koch, S (1953) *Gyermekgyógyászat*, 4, 314
537. Véli, G (1953) *Gyermekgyógyászat*, 4, 311

Czechoslovakia

538 Doleček, R (1952) *Čas Lék čes*, 91, 149
539 Feix, Č, Rezler, D & Šilink, K (1949) *Čas Lék čes*, 88, 845
540 Feix, Č Rezler, D & Šilink, K (1949) *Čas Lék čes*, 88, 1482
541. Fleischhans, B (1948) *Čas Lék čes*, 87, 493
542 Horáčková, M & Pokorny, M (1951) *Čas Lék čes*, 90, 799
543. Hostomská et al (1954) *Čas Lék. čes*, 93, 1064
544 Klima, J. (1934) *Čas Lék čes*, 73, 141
545 Kouba, K (1956) *Čsl Pediat*, 11, 446
546 Langer, P (1956) *Dokl preventiv Starostliv Endokr*, p 33
547 Langer, P. (1957) *Čsl Gastroent Výž*, 11, 318
548 Langer, P, Sedlák, J & Michajlovskij, N (1958) In *Problémy Endokrinologickej Praxe z Hľadiska Výskumu*, Bratislava, p 9
549 Langer, P et al (1958) *Arch Sci med*, 105, 257
550 Németh, Š (1953) *Bratisl lek Listy*, 33, 661
551 Németh, Š & Podoba, J (1955) *Bratisl lek Listy*, 35, 13
552 Nemeth, Š & Štukovsky, R. (1958) *Čsl Pediat*, 13, 97
553 Podoba, J (1953) *Bratisl lek Listy*, 33, 309
554. Podoba, J (1956) *Dokl preventiv Starostliv Endokr*, p 11
555 Podoba, J, Nemeth, S & Grmelová, M (1950) *Bratisl lek Listy*, 30, 397
556. Podoba, J et al (1957) *Bratisl lek Listy*, 37, 67
557 Reisenauer, R & Likar, O (1958) *Čsl Hyg*, 3, 355
558 Reisenauer, R, Šilink, K & Rohling, S (1956) *Sborn lek*, 58, 77
559 Reisenauer, R, Šilink, K & Rohling, S (1959) *Čas Lék čes*, 98, 499
560 Šilink, K & Maršiková, L (1951) *Nature (Lond)*, 167, 528
561 Šilink, K. & Reisenauer, R (1957) *Čas Lék čes*, 96, 809
562 Šilink, K, Reisenauer, R & Chaloupský, J (1959) *Rev Czech Med*, 5, 73
563 Šilink, K et al (1957) *Čas Lék čes*, 96, 1509
564 Slovenská Akademie Věd a Umění (1951) *Research on goitre in Slovakia · some results from the area of Banska Bystrica*, Bratislava
565 Stukovský, R et al (1960) *Vet Med (Praha)*, 5, No 2, p 129
566 Štukovský, R et al (1960) *Vet Med (Praha)*, 5, No 2, p 143
567 Suk, V (1931) *Anthropologie (Praha)*, 9, No 1, p 1
568 Tománek, E (1935) *Bratisl lek Listy*, 15, Suppl No 7, p 128
569 Verner, M (1958) In *Problémy Endokrinologickej Praxe z Hľadiska Vyskumu*, Bratislava, p 43
570 Vohnout, C S & Pihar, O (1950) *Čas Lék čes*, 89, 579
571. Vomela, S (1929) *Rev Neurol Psychiat (Praha)*, 26, 81
572. Vomela, S (1932) *Ann Méd*, 32, 461

Germany

573 Albeaux-Fernet et al (1945) *Bull Soc méd Hop Paris*, 61, 434
574. Aschoff, L (1935) *Arch Kinderheilk*, 105, 159
575 Balks, R (1935) *Landw Jb*, 81, 939
576 Bauer, J. (1952) *Med Klin*, 47, 530
577 Bauer, J. & Hilpoltsteiner (1951) *Endokrinologie*, 28, 260
578 Bauer, J & Wagner, H (1951) *Endokrinologie*, 28, 142
579 Bergfeld, W (1951) *Verh dtsch Ges inn Med*, 57, 138
580 Blum, F. (1925) *Munch med Wschr*, 72, 1010
581. Breitner, B (1926-27) *Mitt Grenzgeb Med Chir*, 40, 288
582 Bukatsch, F, Haubold, H & Lackner, F (1951) *Klin Wschr*, 29, 450
583 Cauer, H (1929) *Z ges phys Ther*, 37, 203

584. Danner, H (1935) *Statistische Erhebungen uber den Kropf und seine geographische Verbreitung im sudlichen Schwarzwald und in der angrenzenden Rheinebene*, Freiburg-im-Breisgau (Thesis)
585 Dieudonné, A. (1928) *Prophylaxe des Kropfes in Bayern* In: *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 540
586 Erfurth, W (1947) *Dtsch GesundhWes*, **2**, 340
587. Erfurth, W (1948) *Dtsch GesundhWes*, **3**, 83
588. Erfurth, W (1951) *Dtsch GesundhWes*, **6**, 1291
589 Feldmann, E. (1928) *Der endemische Kropf der norddeutschen Tiefebene* In *Comptes rendus de la Conference internationale du goitre, Berne, 24-26 août 1927*, Berne, p 90
590 Fischer, E (1950) *Arch Kinderheilk.*, **138**, 199
591. Fuchs, R (1950) *Dtsch med Wschr*, **75**, 1076
592 Fuchs, R. (1952) *Praxis*, **41**, 1026
593. Gloel (1934) *Z MedBeamte*, **47**, 22
594. Grimm, H (1948) *Dtsch GesundhWes*, **3**, 449
595 Grimm, H (1949) *Dtsch GesundhWes*, **4**, 337
596 Habermann, P (1949) *Med Klin*, **44**, 1609
597 Habermann, P (1953) *Kinderarztl Prax*, Sonderheft, p 176
598. Habermann, P (1956) *Kropf und Landschaft*, Leipzig
599 Habermann, P (1957) *Med Klin*, **52**, 1992
600 Haubold, H (1950) *Munch med Wschr*, **92**, 329, 429
601 Haubold, H (1951) *Verh dtsch Ges inn Med*, **57**, 112
602 Haubold, H (1954) *Landw Forsch*, Sonderheft 5, p 59
603 Haubold, H (1955) *Der Kropf, eine Mangelerkrankung*, Stuttgart-Plieningen
604 Heilmann, P (1924) *Virchows Arch path Anat.*, **251**, 361
605 Hesse, E (1911) *Dtsch Arch klin Med*, **102**, 217
606. *J Amer med Ass*, 1948, **138**, 448
607 Jager, H (1938) *Dtsch Arch klin Med*, **182**, 300
608 Klein, F (1937) *Öff GesundhDienst (A)*, **2**, 868
609 Lang, Th (1935) *Zur Aetiologie des endemischen Kropfes* In *Verhandlungsbericht, Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, Bern, p 567
610 Leicher, F (1951) *Virchows Arch path Anat*, **320**, 404
611 Ligdas, E (1953) *Dtsch GesundhWes*, **8**, 1025
612. Marmann (1929) *Veröff MedVerw*, **30**, 313
613. May, R (1940) *Z ges exp Med*, **107**, 450
614. Meiklejohn, A P (1948) *Lancet*, **2**, 619
615 Meinck, F (1927) *Kleine Mitt. Ver Wasser- u Lufthyg*, **3**, 10
616 Meisenburg, J (1952) *Zbl Chir*, **77**, 2351
617. Olesen, R. (1933) *Publ Hlth Rep (Wash)*, **48**, 1074
618. Orth (1927) *Hess Ärztebl*, No 12
619. Otto, H. (1954) *Z ges inn Med*, **9**, 113
620 Pfluger, H (1927) *Arch soz Hyg*, new series, **2**, 525
621. Sakobielski, W. (1949) *Dtsch med Wschr*, **74**, 1210
622. Scheurlen, von (1925) *Z. Hyg InfektKr*, **105**, 45
623 Schittenhelm, A. & Weichardt, W (1912) *Munch med Wschr*, **59**, 2622
624 Schroeder, H (1925) *Angew. Bot*, **7**, 9
625. Sommerfeld, R. (1930) *Z MedBeamte*, **43**, 9
626 Sommerfeld, R et al (1927) *Veroff MedVerw*, **13**, 305
627 Widdowson, E. M. & McCance, R A. (1954) *Studies on the nutritive value of bread and on the effect of variations in the extraction rate of flour on the growth of undernourished children*, London (*Spec Rep Ser med Res. Coun (Lond)*, No. 287)
628 Zacher, K. (1949) *Zbl. Chir*, **74**, 1020

Switzerland

629. Bayard, O (1937) *Schweiz med Wschr*, 67, 1093
630 Bircher, H. (1886) *Die Rekrutierung und Ausmusterung der schweizerischen Armee*, Aarau
631. De Josselin de Jong, R (1946) *Ned T Geneesk*, 90, 1739
632. Demole, V. (1951) *Bull schweiz Akad med Wiss*, 7, 430
633 Dieterle, T & Eugster, J (1933) *Arch Hyg (Berl)*, 111, 136
634 Dieterle, T, Hirschfeld, L & Klinger, R (1913) *Arch Hyg (Berl)*, 81, 128
635. Dind, E (1939) *Endemie goitreuse et prophylaxie par le sel iodé dans le canton de Vaud*, Lausanne (Thesis)
636 Eggenberger, H (1933) *Bull eidg GesundhAmt*, No 18, Suppl. 9
637 Eggenberger, H & Messerli, F M. (1938) In *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, p. 64
638 Eggenberger, H & Messerli, F M (1939) *West J Surg*, 47, 596
639 Eugster, J (1933) *Schweiz Z Hyg*, 13, 313
640 Eugster, J (1935) *Ther d Gegenw*, 76, 115
641 Eugster, J (1936) *Arch Klaus-Stift VererbForsch*, 11, 369
642 Eugster, J. (1938) In. *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, p 130
643 Fellenberg, T von (1933) *Mitt Lebensmitt*, 24, 123
644 Fellenberg, T von (1938) *Mitt Lebensmitt*, 29, 290
645 Graemiger, O (1933) *Schweiz Z Hyg*, 13, 230
646 Hammerli, M (1931) *Schweiz med Wschr*, 61, 881
647. Hunziger, H (1918) *KorrespBl schweiz Ärz*, 48, 220
648 Jordi, A (1939) *Schweiz med Wschr*, 69, 348
649 Lauener, P. (1936) *Schweiz med Wschr*, 66, 207
650 Lauener, P (1939) *Schweiz med Wschr*, 69, 455
651 Lind, S C (1934) *Bull Acad Med Cleveland*, 18, No 7, p 7
652. Messerli, F M (1939) *Rev Hyg Police sanit*, 61, 321
653. Messerli, F M (1952) *Gesundh u Wohlf*, 32, 561
654. Milt, B (1931) *Schweiz med Wschr*, 61, 280
655 Nicod, J L (1940) *Rev med Suisse rom*, 60, 591
656 Nicod, J. L. (1952) *Rev méd Suisse rom*, 72, 646
657 Nicod, J. L (1953) *Bull Wld Hlth Org*, 9, 259
658 Nicod, J. L (1957) In *Le Tireopatie*, Torino, vol 5, pp 165-220
659. Olesen, R (1933) *Publ Hlth Rep (Wash)*, 48, 651
660 Oswald, A & Risch, W (1939) *Munch med Wschr*, 86 996
661. Richard, M (1951) *Praxis*, 40, 1
662. Risch, W (1939) *Wien Arch inn Med*, 33, 1, 127, 197
663 Ryncki, P. (1952) *Contribution a l'étude de l'endemie goitreuse*, Lausanne (Thesis)
664 Schamaun, H M (1954) *Helv paediat Acta*, 9, 455
665 Schaub, F A (1949) *Über Erfolge der Kropfprophylaxe*, Zürich (Thesis)
666 Stiner, O (1924) *Bull eidg GesundhAmt*, No 6, Suppl No 4, p 23
667 Stiner, O (1924) *Schweiz med Wschr*, 54, 391
668 Stiner, O (1928) *Schweiz med Wschr*, 58, 401
669 Stiner, O. (1928) *Zur Verbreitung des endemischen Kropfes in der Schweiz* In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 403
670 Thalmann, A (1954) *Schweiz med Wschr*, 84, 473
671 Vontobel, V (1956) *Der Neugeborenenkropf*, Zurich (Thesis)
672 Walthard, B (1952) *Schweiz med Wschr*, 82, 423
673 Wegelin, C (1945) *Presse méd*, 53, 514
674 Wespi, H J (1948) *Schweiz. med Wschr*, 78, 130

675. Wespi, H J. (1950) *Wien klin Wschr*, 62, 21, 40
676 Wespi, H J (1954) *Praxis*, 43, 616
677. Wespi, H. J. (1954) *Schweiz med Wschr*, 84, 885
678 Wespi, H J (1956) *Münch. med Wschr*, 98, 1150
679. Wespi, H J & Eggenberger, H U. (1954) *Rückblick und Ausblick nach 30 Jahren Kropfprophylaxe in der Schweiz*, Aarau & Herisau
680. Wespi, H. J & Eggenberger, H U. (1957) *Bull eidg Gesundh.-Amt.*, June 1, Beilage B, No 4
681 Wespi, H J & Schaub, F (1950) *Vjschr schweiz SanitOff.*, 27, No 2, p 56
682. Wohlfender, P (1950) *Untersuchungen über den endemischen Kropf bei Primarschülern des Kantons Thurgau in den Jahren 1946 und 1949*, Zurich (Thesis)

Italy, Sicily and Sardinia

683. Ambrosi, V (1937) *Rass. int Clin Ter*, 18, 839
684 Ambrosi, V (1938) *Rev Hyg. Police sanit*, 60, 412
685. Ambrosi, V (1941) *Policlinico, Sez prat*, 48, 1608
686 Anglesio, E. (1942) *Il gozzo acuto*, Torino, pp. 13-22
687 Bagnasco, S (1935) *G Psichiat Neuropat*, 63, 193
688. Balice, A (1948) *Ann Igiene*, 58, 33
689 Balice, A. (1949) *Ann Sanità pubbl*, 10, 731
690 Balp, S (1923) *G Accad Med Torino*, 4th series, 29, 117
691. Barbieri, G (1958) *Igiene San pubbl*, 14, 516
692. Bertoli, P (1932) *Ann Igiene*, 42, 231
693 Bizzarri, O (1951) *Rass. int. Clin Ter*, 31, 357
694 Buonomini, G & Imbasciati, B (1957) In *Le Tireopatie*, Torino, vol 5, pp 445-516
695. Businco, L (1937) *Scr biol Luigi Castaldi*, 12, 79
696. Businco, L & Antoniotti, F (1947) *Rass Neurol veg*, 6, 269
697. Calbi, M (1948) *Ann Igiene*, 58, 97
698. Cancellara, E. (1949) *Ann Sanità pubbl*, 10, 741
699 Cancellara, E (1952) *Ann Sanita pubbl*, 13, 1595
700 Cavatorti, P (1907) *Il gozzo in Italia*, Parma
701 Cerletti, U (1935) *Tre anni di ricerche sperimentali sulla etiologia del gozzismo endemico* In. *Verhandlungsbericht, Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, Bern, p. 501
702. Cerletti, U (1951) *Sperimentale*, 100, 544
703 Cerletti, U (1958) *Arch. Sci med*, 105, 91
704. Cerruti, C F (1938) *Rev Hyg. Police sanit*, 60, 426
705. Ciocchi, A (1957) *Ann Sanità pubbl*, 18, 93
706. Ciocchi, A (1958) *Ann Sanita pubbl*, 19, 333
707. Ciocchi, A (1958) *Arch Sci med*, 105, 117
708. Coppola, A. (1930) *Riv. Pat. nerv ment*, 35, No 1, 232
709 Corda, D. (1935) *Clin pediat (Modena)*, 17, 725, 787
710. Costa, A (1956) *Rev ibér. Endocr*, 3, 139
711. Costa, A. (1959) *Ann Endocr (Paris)*, 20, 435
712. [illegible] (1960) [illegible] *Org*, 22, 493
713. [illegible]
714. [illegible]
715 [illegible]
716. [illegible] vol 5, pp. 327-404
717. [illegible]
718. [illegible]
719. D'Alo, G. (1947) *Riv ital Igiene*, 7, 344
720 D'Amora, T. (1941) *Pediatria (Napoli)*, 49, 82
721. D'Attilio, E. (1958) *Arch Sci med*, 105, 135

722. [illegible]
723. [illegible]
724. [illegible] 49, 2964
725. [illegible]
726. [illegible]
727. Di Porto, A & Antoniotti, F. (1947) *Policlinico, Sez prat*, **54**, 1182
728. Ferraris, G M. et al (1959) *Folia endocr (Pisa)*, **12**, 84
729. Ferrini, O. et al. (1957) *Arch E. Maragliano Pat Clin*, **13**, 1265
730. Ferrini, O et al (1958) *Arch Sci med*, **105**, 205
731. Ferrua, M (1942) *Quad Nutr.*, **8**, 181
732. Fiorio, G (1949) *Arch De Vecchi Anat patol*, **13**, 961
733. [illegible] *med*, 105, 215
734. [illegible]
735. [illegible]
736. [illegible]
737. Lacroix, L & Cravetto, C. (1958) *Arch. Sci med*, **105**, 243
738. Lutrario, A (1934) *Bull Off int Hyg publ*, **26**, 1569
739. Maggia, O & Ravera M. (1946) *Pediat Med prat*, **19-21**, 455
740. Maggiorotti, U. (1946) *Minerva med (Torino)*, **2**, 14
741. Magherini, G & Zecchi, A M (1955) *Rass Studi psichiat*, **44**, 259
742. Magherini, G et al (1956) *Riv Clin pediat*, **57**, 929
743. Marchesa, A (1935) *Considerazioni e rilievi sulle ipertrofie della tiroide nella Provincia di Imperia* In *Verhandlungsbericht, Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, Bern, p 545
744. Massucco Costa, A (1957) In *Le Tireopatie*, Torino, vol 5, pp 837-838
745. Massucco Costa, A (1958) *Arch Sci med*, **105**, 169
746. Menicucci, M (1942) *Policlinico, Sez prat*, **49**, 1223
747. Monneret, A M (1928) *Ricerche sull'etiologia del gozzo* In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 464
748. Mortara, M (1946) *Arch Sci med*, **81**, 160
749. Mortara, M (1948) *Epidemie gozzigene*, Torino
750. Mortara, M (1957) *In Le Tireopatie, Torino, vol 5, pp 59-140*
751. Mortara, M & Martinetti, L (1957) *Folia endocr (Pisa)*, **10**, 191
752. Mucci, A (1934) *Arch ital Sci med colon*, **15**, 285
753. Muggia, G (1928) *La profilassi del gozzo endemico* In *Comptes rendus de la Conference internationale du goitre, Berne, 24-26 août 1927*, Berne, p. 486
754. Muggia, G (1931) *Rass Studi psichiat*, **20**, 959
755. Muggia, G (1933) *Rass Studi psichiat*, **22**, 718
756. Mu [illegible]
757. Na [illegible]
758. Paccagnella, B (1953) *Ann Sanità pubbl*, **14**, 115
759. Pighini, G (1920) *Riv sper Freniat*, **44**, 409
760. [illegible]
761. [illegible]
762. [illegible] o, vol. 4,
763. [illegible]
764. [illegible]
765. [illegible]
766. Previtera, L, Molino, G & Pagano, V (1958) *Arch Sci med*, **105**, 253
767. Raggi, P. & Marocco, F (1958) *Arch Sci med*, **105**, 273
768. Raggi, P. & Marocco, F (1958) *Folia endocr (Pisa)*, **11**, 191
769. Sainsbury, H (1945) *Med Offr*, **73**, 207

770 Sapori, C. (1954) In. *Le Tireopatie*, Torino, vol 4, pp 217-220
771 Sardinia, Commissione nominata d'ordine di S M il re di Sardegna per studiare il cretinismo (1848) *Relazione della commissione* , Torino
772 Scocciantí, R. (1940) *Policlinico, Sez prat*, 47, 1081
773 Spadaro, O & Alfano, G (1955) *Igiene San pubbl*, 11, 395
774 Tarozzi, G (1958) *Ann Sanità pubbl*. 19, 165
775 Tempestini, O (1957) *Clinica Odontoiatrica*, 12, 10
776 Trikurakis, G (1935) *Contributo allo studio dell'etiologia del gozzo Ricerche in zona endemica montana*. In *Verhandlungsbericht*. *Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, Bern, p 524
777 Trikurakis, G A. (1939) *Arch Sci med*, 67, 649
778. Trikurakis, G A (1940) *Policlinico, Sez prat*, 47, 87
779. Turletti, G. (1951) *Riv. ital Igiene*, 11, 118, 191
780 Turri, E (1957) *Ann Sanità pubbl*, 18, 1421
781 Vogliazzo, U & Forni, P V. (1948) *Arch Sci med*, 86, 511
782 Vogliazzo, U & Viale, G. (1952) In. *Le Tireopatie*, Torino, vol 2, pp 227-234

Spain

783 Altava, V., Royo, M. & Gomez, E. (1959) *El bocio endémico en la Provincia de Castellon*, Castellón de la Plana
784 Andreu Urra, J., Rivero Fontán, J L. & Stiefel Barba, E (1955) *Rev ibér. Endocr.*, 2, 747
785 Draper Alfaras, J (1929) *Rev méd Barcelona*, 11, 512
786. Eugster, J & Dieterle, R (1952) *Helv chir Acta*, 19, 527
787 Greenwald, I. (1958) *Bull Hist Med*, 32, 121
788 Ibáñez González, R. et al (1956) *Rev. clin esp*, 61, 285
789 Ibáñez González, R et al (1959) *Rev Sanid Hig públ (Madr)*, 33, 157
790 Legendre, M (1927) *Las Hurdes Etude de géographie humaine*, Bordeaux
791. Marañón, G (1927) *El bocio y el cretinismo · su patogenia y epidemiología en Espagna*, Madrid
792 Marañón, G (1928) *Résume de l'état actuel du probleme du goitre endemique en Espagne* In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 389
793 Martin Hoyos, G (1958) *Rev ibér Endocr*, 5, 157
794 Martin Lázaro, J M (1958) *Rev. clin esp.*, 68, 302
795 Morreale de Castro, G et al. (1953) *Rev clin. esp.*, 50, 285
796 Morreale de Castro, G et al (1954) *Rev clin esp*, 52, 247
797 Ortiz de Landázuri, E (1954) *Rev ibér Endocr.*, 1, 317
798 Ortiz de Landazuri, E. & De la Higuera Rojas, J (1949) *Rev clin. esp*, 32, 234
799 Ortiz de Landázuri, E, De la Higuera Rojas, J & Mora Lara, R (1947) *Rev. clin esp*, 26, 357
800. Ortiz de Landázuri, E, Ortega Bernárdez, A & Galdo Seco, A (1948) *Rev clin esp*, 30, 148
801 Ortiz de Landázuri, E & Palenzuela, J M (1948) *Rev clin. esp*, 30, 77
802 Ortiz de Landázuri, E & Palenzuela, J M (1949) *Rev clin. esp*, 32, 311
803. Ortiz de Landázuri, E et al. (1948) *Rev clin esp*, 28, 304
804. [illegible] *esp*, 28, 369
805. [illegible] *sp*, 40, 372
806 [illegible] *sp*, 53, 24
807. [illegible] andazuri, E (1950) *Rev clin esp*, 39, 27
808 Palenzuela, J M, Ortiz de Landazuri, E & Mora Lara, R. J. (1950) *Rev. clin esp*, 37, 156
809. Perez-Vitoria, C (1955) *An Med. (Med)*, 41, 104

810 Piulachs, P & Cañadell, J M. (1950) *Enfermedades del tiroides*, Barcelona
811. Rivero Fontán, J L. & Stiefel Barba, E (1954) *Hisp. méd*, 11, 94
812. Rodríguez Moreno, F. (1955) *Aspectos del estado actual del bocio en España*, Granada (Thesis)
813. Rodríguez Moreno, F., Ibáñez Gonzalez, R. & Ortiz de Landázuri, E. (1956) *Rev clin esp*, 60, 154
814. Ruiz Martín, M et al (1950) *Rev clin. esp*, 39, 107
815 Ruiz Martin, M et al (1954) *Rev clin esp*, 53, 89

Portugal

816 De Almada Lencastre Cruz de Campos, F. R (1950) *Relatorio do Serviço Tecnico de Higiene da Alimentação e Bromatologia para o Ano de 1949*, Lisbon, p 51
817 Teixeira Basto, A (1907) *O bócio em Portugal Cirurgia e distribuição geografica*, Oporto

Belgium

818. Bastenie, P A (1947) *Lancet*, 1, 789
819 Brull, L. (1942) *Bull Acad Med. Belg*, 6th series, 7, 23
820 Brull, L (1950) *Rev med Liege*, 5, 1
821 Brull, L (1950) *Rev méd Liege*, 5, 25
822. Brull, L (1950) *Rev. méd Liege*, 5, 177
823 Brull, L (1950) *Rev med Liege*, 5, 206
824 Brull, L (1950) *Rev méd Liege*, 5, 229
825 Brull, L. (1950) *Rev méd Liege*, 5, 261
826 Brull, L & Dewart, L (1956) *Rev méd Liège*, 11, 653
827 Brull, L & Lefebvre, L. (1950) *Rev méd Liege*, 5, 353
828 Clinquart (1926) *Bull Acad Méd Belg.*, 5th series, 6, 505
829 De Moor, P (1955) *Acta chir. belg*, 54, 694
830 Sand, R (1946) *Arch belges Méd soc*, 4, 7
831 Thomas, F (1933) *C R Soc Biol (Paris)*, 112, 217

England and Wales

832. Addison, W (1836) *Trans prov med surg Ass*, 4, 87
833 Ash, W M (1926) *J State Med*, 34, 627
834 Austin, J B (1822) *Lond med phys J*, 48, 298
835 Bayers, W (1824) *Edinb med surg J*, 22, 320
836 Berry, J (1901) *Diseases of the thyroid gland and their surgical treatment*, London, pp 57-65
837 Black, J (1837) *Trans prov med surg Ass*, 5, 125
838 Blower, W (1857) *Brit med J*, p 924
839 Campbell, J M H (1927) *J Hyg (Lond)*, 26, 1
840 Cochrane, A. L & Miall, W E (1956) *Proc roy. Soc Med*, 49, 261
841 Cooke, R. T (1953) *Lancet*, 2, 298
842 Curnow, R N (1948) *Annual report of the School Medical Officer, Cornwall County Council (Education Committee), for the year 1947*, Truro, p 8
843 Currie, J (1871) *Glasg med J*, new series, 3, 153
844 Davies, I J & Rogers, L (1940) *Brit med J*, 1, 764
845 Drug, T D (1825) *Lond med phys J*, 53, 49
846 Durham, H E (1921) *J Hyg (Lond)*, 19, 394
847. Fagge, G H (1871) *Med-chir Trans*, 54, 155
848 Forbes, J (1836) *Trans prov. med surg Ass*, 4, 152
849 Garner, R (1844) *The natural history of the county of Stafford, comprising its geology, zoology, botany and meteorology also its antiquities, topography, manufactures, etc*, London, p 47

850 Great Britain, Medical Research Council, Goitre Subcommittee (1944) *Lancet*, 1, 107
851 Guggenbühl (1851) *Lond. med Gaz (J pract Med.)*, new series, 12, 1054
852 Hoey, R A (1950) *Incidence of goitre in the Bedwellty urban district*, Aberbargoed (Report of the Medical Officer of Health, Bedwellty Urban District Council)
853 Holbrook, J (1817) *Lond med Repository, Monthly J & Rev.*, 8, 288
854 Hughes, D E, Rodgers, K & Wilson, D C (1958) *Proc. Nutr. Soc*, 17, xxxiv
855 Hughes, D E, Rodgers, K & Wilson, D C (1959) *Brit med J.*, 1, 280
856 Inglis, J (1838) *Treatise on English bronchocele, with a few remarks on the use of iodine and its compounds*, London
857. Jeffery, J D (1843) *Trans prov med surg Ass*, 11, 157
858 Kemp, F H. & Wilson, D C (1946) *Lancet*, 1, 172
859 *Lancet*, 1860, 1, 62
860 Lebour, G A (1881) *Med. Tms & Gaz*, 2, 492
861 Lisney, A A (1951) *Brit med J*, 1, 474
862 Low, R. B (1878) *Brit med J*, 1, 932
863 Low, R. B (1882) *Brit med J*, 1, 43, 80
864 Mackenzie, M (1877) *Med Examr*, 2, 854
865 Manson, A (1825) *Medical researches on the effects of iodine in bronchocele, etc.*, London
866 Martin, J M (1936) *Annual report of the County Medical Officer of Health, Gloucestershire*
867 Milligan, E H M (1926) *Brit med J*, 2, 373, 577, 758
868 Moffat, T (1870) In *Reports of the British Association, Liverpool Meeting, 1870, Transactions of Sections*, p 80
869 Murray, M M. & Wilson, D C (1945) *Nature (Lond)*, 155, 79
870 Murray, M M & Wilson, D C (1945) *Lancet*, 2, 23
871 Murray, M M et al (1948) *Thyroid enlargement and other changes related to the mineral content of drinking water (with a note on goitre prophylaxis)*, London (Medical Research Council Memorandum No. 18)
872 Nash, D. W (1838) *Trans prov med surg Ass*, 6, 251
873 Norris, H (1847-48) *Med. Tms (Lond)*, 17, 257
874. Orr J B (1931) *Report to the Nutrition Committee of the Medical Research Council on the correlation between iodine supply and the incidence of endemic goitre*, London (*Spec Rep Ser med Res Coun (Lond)*, No. 154)
875 Rees, G A. (1851) *Lond med Gaz (J pract Med)*, new series, 13, 158
876 Reeve, H (1809) *Edinb med surg J*, 5, 31
877 Roberts, C (1882) *Brit med. J*, 1, 117
878. Rumsey, N (1844) *Prov med surg J*, 8, 185
879 Savage, G H (1872) *Lancet*, 2, 77
880 Shapter, T. (1842) *Trans prov med surg Ass*, 10, 107
881 Simpson, A (1951) *Brit med J*, 1, 588
882 Stevenson, L E. (1898) *On the occurrence of endemic goitre in Cumberland and Westmoreland, with some observations on the etiology of the disease*, Cambridge
883. Stocks, P (1928) *Quart J Med*, 21, 223
884 Taylor, D O (1935) *Med Offr*, 54, 133
885 Taylor, S (1958) *Lancet*, 1, 751
886 Turton, P H J (1926) *Brit med J.*, 2, 501, 614
887. Turton, P. H J (1933) *Proc. roy. Soc Med*, 26, 1223
888. Ward, T O (1841) *Trans prov. med surg Ass*, 9, 247
889. Watson, K. (1834) *Trans. prov med surg Ass*, 2, 181
890 White, J. (1853) *Trans prov. med surg. Ass*, new series, 7, 171
891. Wilson, D C. (1945) *J. Hyg (Lond)*, 44, 221
892. Wilson, E. (1947) *Lancet*, 2, 70
893 Wood, K. (1824) *Mem lit. phil. Soc. Manchester*, new series, 4, 83

894 Young, M, Crabtree, M G & Mason, E. M (1936) *The relationship of the iodine contents of water, milk and pasture to the occurrence of endemic goitre in two districts of England*, London (*Spec Rep. Ser med Res Coun* (*Lond*), No 217)

Scotland

895 Keddie, J A G (1954) *Deaf-mutes in Scotland*, Edinburgh (Department of Health for Scotland)
896 Mackay, N D. (1914-17) *Caledon med. J.*, **10**, 71
897 Mackay, N D (1914-17) *Caledon med J*, **10**, 254
898. McKenzie, D (1899) *Glasg med J*, **51**, 15
899. Marshall, H (1832) *Edinb med surg J*, **38**, 330
900 Mitchell, A (1862) *Brit for med-chir Rev*, **29**, 502
901 Ogilvy, S G. (1911) *An investigation into the prevalence of endemic goitre in Fauldhouse and neighbourhood*, Edinburgh (Thesis)
902 Reid, J (1836) *Edinb med surg J*, **46**, 40
903 Sloan, A T (1883) *Edinb med J*, **29**, 30

Northern Ireland

904 Erskine, F M (1933) *J State Med*, **41**, 672
905 Erskine, F. M (1942) *Ulster med J*, **11**, 108
906 Olesen, R & Neal, P A (1930) *Publ Hlth Rep* (*Wash*), 45, 2669

Ireland

907. Mason, E. M, O'Donovan, E M & Kilbride, D (1945) *An enquiry into the cause of goitre in County Tipperary An investigation of iodine contents of foodstuff, soil and drinking water of that county compared with others of less goitrous counties in Ireland* (Unpublished report of the Medical Research Council of Ireland)
908 Naughten, M (1949) *Irish J. med Sci*, 6th series, No 281, p 197
909 Naughten, M & Shee, J C (1939) *Irish J med Sci*, 6th series, No 160, p. 164
910 O'Donovan, D K (1950) *Irish J med Sci*, 6th series, No 293, p 161
911. O'Shea, E. M (1946) *Irish J med Sci*, 6th series, No 251, p 749
912 Shee, J C (1939) *Irish J med Sci*, 6th series, No 167, p 802
913 Shee, J C (1939) *Report of the goitre survey in South Tipperary for the Medical Research Council of Ireland*, Cork
914. Shee, J C. (1940) *Sci Proc roy. Dublin Soc*, new series, **22**, 307

France

915. Ancelon, E-A (1850) *Mémoire sur les causes du goître et du cretinisme endémiques a Rosières-aux-Salines*, Nancy
916 Baillarger, J G F (1862) *C R. Acad Sci* (*Paris*), 55, 475
917 Baillarger, J G F. (1863) *Rec Méd vet*, **40**, 133
918 Bérard, L & Dunet, C (1928) *Rapport sur l'étiologie et l'épidémiologie du goitre endémique en France.* In *Comptes rendus de la Conference internationale du goitre, Berne, 24-26 août 1927*, Berne, p. 276
919 Berger, C-J (1868) *Du crétinisme et du goitre endémiques, notamment dans le departement de l'Ain*, Bourg
920 Bergeret, d'A (1864) *Le goître dans le Jura*, Lons-le-Saunier
921. Blechmann, G (1934) *Concours méd*, **56**, 1033
922 Borrel, A, Boez, L & Freysz (1925) *C. R Soc Biol* (*Paris*), **92**, 232
923 Bourgeat, F (1914) *Le goitre dans le Jura répartition géographique Essai de pathogenie et de prophylaxie*, Paris (Thesis)
924 Darnis (1869) *Etude sur le goître et le crétinisme dans le Tarn-et-Garonne*, Montauban

925 Darré-Larbonne, P (1830) *Dissertation sur le goître, considéré comme endémique dans la vallée de Bigorre, précédée d'un léger aperçu de la topographie médicale de cette contrée*, Paris (Thesis)
926 Dourif, G -H (1862) *Note sur quelques cas de goître aigu ou estival épidémique observés a l'Hôtel-Dieu de Clermont-Ferrand, aux mois d'août et de septembre 1860*, Clermont-Ferrand
927 Faugere & Vichnevsky (1949) *Bull Inst nat Hyg (Paris)*, 4, 471
928 Freyss, M (1941) *Progr méd (Paris)*, 69, 855
929 Fuster (1866) *Du goître dans le département de la Haute-Savoie. Rapport de la commission médicale instituee par arrêté préfectoral du 20 août 1866*, Annecy
930 Gleizes, L & Boy, J (1958) *Concours méd*, 80, 4675
931 Gleizes, L & Boy, J (1958) *Travaux de l'Association de Médecine Rurale*, p 38
932. Guy & Dagand (1863) *Du goître et du crétinisme dans le département de la Haute-Savoie, et des moyens pratiques les plus propres à combattre cette affection*, Annecy
933 Jacob, Y (1940) *Contribution à l'étude du goitre l'hypertrophie des thyroïdes chez le poulain côtier breton*, Paris (Thesis)
934 Jacques, L. (1894) *Contribution a l'étude du goître dans les Hautes-Alpes*, Lyon
935 *J Amer med Ass*, 1934, 102, 1691
936 Laroche, G, Milhaud, F & Vichnevsky, I. (1959) *Bull. Inst nat Hyg (Paris)*, 14, 967
937 Laroche, G, Tremolieres, J & Vichnevsky, I (1953) *Bull Inst nat Hyg. (Paris)*, 8, 445
938 Laroche, G et al (1951) *Bull Inst nat Hyg (Paris)*, 6, 261
939 Marc
l'
940 Marc
l'.
No 17)
941 Mayet, L (1900) *Arch gén Méd*, new series, 4, 179
942 Mayet, L (1900) *Mém Soc Sci med Lyon*, 40, 21
943 Mayet, L (1901) *Bull Soc Anthropol Paris*, 5th series, 2, 431
944 Mayet, L (1908) *C R Ass franç Avanc Sci*, 37, 701
945 Morel (1851) *Considérations sur les causes du goître et du crétinisme endémiques à Rosières-aux-Salines*, Nancy
946 Mouriquand, G & Enselme, J (1945) *Presse méd*, 53, 533
947 Rhein, M (1935) *Répartition géographique du goitre endémique et nappe d'eau souterraine* In *Verhandlungsbericht, Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, p 481
948 Rochaix, A (1938) *Rev Hyg Police sanit*, 60, 401
949 Roynard (1909) *Bull Soc cent Méd vét*, 63, 450
950 Tourdes, G (1854) *Du goître à Strasbourg et dans le département du Bas-Rhin*, Strasbourg
951. Vichnevsky, I (1949) *Bull Acad. nat Méd (Paris)*, 3rd series, 133, 363
952 Vichnevsky, I (1950) *Sem Hôp Paris*, 26, 1503
953 Vingtrinier (1854) *Du goître endémique dans le departement de la Seine-Inférieure, et de l'étiologie de cette maladie*, Rouen
954.
955

Africa (general)

956. Greenwald, I (1949) *Bull Hist Med*, 23, 155
957. Guinet, P & Berger, M (1953) *Lyon méd*, 188, 253

Algeria

958 Bernard, P. (1955) *Contribution à l'etude du goitre endémique en Algérie*, Alger (Thesis)

959. Goinard, P. (1958) *Algérie méd*, 62, 257

960 Sergent, E (1912) *Bull Soc. Path exot*, 5, 122

961 Seror, J et al (1955) *Afr franç chir*, 13, 269

962 Vergoz, C, Boulard, C. & Bernard, P. (1955) *Algérie méd*, 59, 697

963 Vergoz, C. & Sicard (1959) *Algérie méd* 63, 707

Morocco

964 Alonso Romeo, V (1946) *Med colon*, 7, 343

965 Leo Africanus (1550) *Descrittione dell'Affrica*, Venezia

966 Manuel Amaro, J (1945) *Med colon.*, 5, 487

967. Murray, M. M & Wilson, D C (1948) *Brit dent. J*, 84, 97

Canary Islands

968 Hernández Feliciano, M (1955) *Rev. clin esp*, 57, 162

969 Hernández Feliciano, M (1957) *La evolución hiperfuncional del bocio endémico*, Madrid (Thesis)

French West Africa

970 Denoix, P (1948) *Bull Inst. nat Hyg (Paris)*, 4, 264

971 Pales, L (1950) *Bull méd Afr occid franç*, 7, 7

972 Pales, L (1950) *Cartes de répartition du goitre endemique en Afrique Occidentale Française (enquête 1948)*, Dakar

973 Pales, L (1950) *Les sels alimentaires*, Dakar

974 Pales, L (1950) *Pathologie comparative des populations de l'A O F 2 Le goitre endémique en A O F d'après l'enquête du Service de Sante en 1948 Faits et hypothèses*, Dakar

975 Pales, L (1951) *Cartes ethniques de l'Afrique Occidentale*, Dakar

976 [illegible]

977. [illegible]

978 Riviere, J (1950) *Bull méd Afr occid franç*, 7, 23

979 Toury, J & Lunven, P (1957) *Bull Soc Path exot*, 50, 712

Gambia

980 Mungo Park (1799) *Travels in the interior districts of Africa, 1795-1797*, London

Sierra Leone

981 Blacklock, D B (1924) *Report on an investigation into the prevalence of goitre in the Protectorate of Sierra Leone*, Freetown

982 Blacklock, D B (1925) *Trans roy Soc trop Med. Hyg.*, 18, 395

983 Blacklock, D B (1930) *Report on a survey of human diseases in the Protectorate of Sierra Leone*, Freetown

984 Campbell, N G D (1950) *Epidemic Diseases Control Unit annual report for 1949*, Kailahun

985 Economic Advisory Council, Committee on Nutrition in the Colonial Empire (1939) *First report. 2 Summary of information regarding nutrition in the Colonial Empire*, London, p 44

986 Laing, A G (1825) *Travels in the Timannee, Kooranko, and Soolima Countries, in Western Africa*, London, p 430

987 McIntyre, A D. (1954) *Communication to Director of Medical Services, Sierra Leone*
988 Wilson, D C et al (1954) *Trans roy Soc. trop Med Hyg.*, **48**, 481

Nigeria

989 Buxton, J et al (1954) *Brit J. Nutr*, **8**, 170
990 Denfield, J (1947) *Brit med J.*, **1**, 323
991 Economic Advisory Council, Committee on Nutrition in the Colonial Empire (1939) *First report 2 Summary of information regarding nutrition in the Colonial Empire*, London, p 40
992. Greenwald, I (1955) *Fed Proc*, **14**, 435
993 Nicol, B (1955) *The present nutritional situation in Nigeria* (Report of the Adviser on Nutrition, Federal Medical Department, Lagos)
994 Tonkin, T J (1905) *Brit med J*, **1**, 396
995 Wilson, D. C (1952) *An investigation of goitre in Nigeria, October 1951-March 1952* (Report to the Medical Department, H M. Colonial Service, London)
996 Wilson, D C (1954) *Brit J Nutr*, **8**, 83
997 Wilson, D C (1954) *Brit J Nutr*, **8**, 90

French Equatorial Africa

998 Bascoulergue, P -R (1958) *Méd trop.*, **18**, 816
999. Bouilliez, M. [& Todd, J -L] (1916) *Bull Soc Path exot*, **9**, 143
1000 Dupont, R (1941) *Presse méd*, **49**, 57
1001 Masseyeff, R (1954) *Le goitre endémique dans l'Est-Cameroun*, Yaoundé
1002 Masseyeff, R (1955) *Bull. Soc Path exot.*, **48**, 269
1003 Muraz, G (1928) *Bull Soc Path exot.*, **21**, 54, 141
1004 Muraz, G (1936) *Presse méd*, **44**, 1761
1005 Muraz, G (1943) *Presse méd*, **51**, 349

Angola

1006 Leitch, J N. (1930) *Dietetics in warm climates*, London, p 389

Egypt

1007 Dolbey, R. V. & Omar, M (1924) *Lancet*, **2**, 549
1008 Ghalioungui, P. (1954) *Endocrines, gout and vitamins*, Cairo
1009 Ghalioungui, P (1955) *Bull clin sci Soc Abbassia Fac Med*, **6**, No 2, p 1
1010 Ghalioungui, P (1957) *Rev ibér Endocr*, **4**, 385
1011 Ghalioungui, P & Shawarby, K (1956) *J Egypt. Soc. Endocr. Metab*, **2**, No 3, p 33
1012. Ibrahim, A (1932) *J Egypt. med Ass*, **15**, 401

Sudan

1013 Ghalioungui, P. et al (1956) *J. Egypt Soc Endocr. Metab*, **2**, No. 3, p 1
1014 Woodman, H (1952) *E Afr med J*, **29**, 217

Ethiopia and Eritrea

1015 Angelini, G & Scaffidi, V (1937) *Folia med (Napoli)*, **23**, 356
1016 Gasperini, G C. (1942) *Boll. Soc. ital. Med Igiene trop.*, **1**, 122
1017. Grassi Bertazzi, C. (1952) *Arch ital Sci med trop*, **33**, 446
1018. Mérab (1912) *Médecins et médecine en Ethiopie*, Paris, pp 41, 165
1019. Nägelsbach, E (1934) *Arch. Schiffs- u Tropenhyg*, **38**, 151
1020. Singer, C. (1905) *J trop Med*, **8**, 17

British Somaliland

1021. Economic Advisory Council, Committee on Nutrition in the Colonial Empire (1939) *First report. 2. Summary of information regarding nutrition in the Colonial Empire*, London, p 12

Uganda

1022. Dean, R F A. (1954) *J trop Med Hyg*, 57, 283

Belgian Congo and Ruanda-Urundi

1023 Baudart, M (1939) *Ann Soc belge Méd trop*, 19, 129
1024 Calonne, R (1939) *Ann Soc belge Méd trop*, 19, 143
1025 Campenhout, E. van (1934) *Bull Off int Hyg publ*, 26, 1564
1026 Daloze, G -A [& Trolli, G] (1933) *Ann Soc belge Méd trop*, 13, 133
1027 Davidson, L S P (1954) *Lancet*, 1, 614
1028 Delaunoy, A & Claeys, A (1957) *Ann Soc belge Méd trop*, 37, 815
1029. Demaeyer, E M & Vanderborght, H L (1953) *Ann Soc belge Méd trop*, 33, 579
1030 De Smet, M P (1954) *Ann Soc belge Méd trop*, 34, 47
1031 De Smet, M P (1956) *Belg T Geneesk*, 12, 521
1032 De Smet, M P (1957) *Docum Med geogr trop (Amst)*, 9, 385
1033 Himpe, N E & Pierquin, L (1950) *Ann Soc belge Méd trop*, 30, 205
1034 *J Amer med Ass*, 1946, 131, 1104
1035 Kadaner, M (1924) *Ann Soc belge Méd trop*, 4, 149
1036 Perin, F (1945) *Rec Sci méd Congo belge*, No 3, p 32
1037 Rodhain, J (1915) *Bull Soc Path exot*, 8, 734
1038 Schotte, A (1931) *Ann Soc Med Gand*, 10, 72
1039 Schotte, A (1931) *Rev belge Sci méd*, 3, 281
1040 Vande Voorde, R R (1956) *Ann Soc belge Méd trop*, 36, 211
1041 Van Riel, J (1958) *Hygiène tropicale*, Liège, p 67
1042 Velghe, A (1954) *Ann Soc belge Méd trop*, 34, 127

The Rhodesias

1043 Affleck, H (1958) *Rhod agric J*, 55, 439
1044 Beet, E A (1951) *Arch Dis Childh*, 26, 119
1045 Southern Rhodesia, Nutrition Council (1959) *Annual Reports for 1957 and 1958*, Gwelo, p 5

Union of South Africa and neighbouring territories

1046 Blom, I J B (1934) *Onderstepoort J vet Sci*, 2, 131
1047 Buttner, E E (1935) *S Afr med J*, 9, 187
1048 Cape of Good Hope, Department of Public Education (1929) *Report of the Superintendent-General of Education*, p 47
1049 Dormer, B A (1940) *Annual report of the Department of Public Health, Union of South Africa*
1050 *Fmg S Afr*, 1956, 32, No 9, p 22
1051 Frack, I (1932) *S Afr med J*, 6, 724
1052 Kark, S L & Le Riche, H (1944) *Manpower (Pretoria)*, 3, No 1, p 2
1053 Kerrich, J E (1951) *S Afr J med Sci*, 16, 39
1054 Le Riche, H (1943) *A health survey of 3,510 African school children in Alexandra township*, Johannesburg
1055 Malherbe, H (1952) *S Afr med J*, 26, 733
1056 Malherbe, H & Osburn, L W (1951) *S Afr J med Sci*, 16, 33
1057 Malherbe, H & Osburn, L W (1951) *S Afr J med Sci*, 16, 49
1058 Matthew, A & Thomas, A D (1935) *J S Afr vet med Ass*, 6, 128
1059 Muñoz, J A & Anderson, M M (1959) *Bull Wld Hlth Org*, 21, 715
1060 Province of Natal (1948) *Report on Medical Inspection*, p 25
1061 Schur Brown, A S (1935) *S Afr. med J*, 9, 251
1062 Steyn, D G (1948) *S Afr med J*, 22, 525
1063 Steyn, D G & Sunkel, W (1954) *J S Afr vet med Ass*, 25, No 4, p. 9
1064 Steyn, D G et al (1952) *Report on an investigation into the occurrence of endemic goitre in the Eastern Caprivi Strip, South Africa*, Pretoria

1065 Steyn, D G et al. (1955) *Endemic goitre in the Union of South Africa and some neighbouring territories*, Pretoria
1066. Union of South Africa, Department of Public Health (1929) *Annual report*, Pretoria, p. 67
1067. Union of South Africa, Department of Public Health (1929) *Pamphlet No. 394 (Health)*, Pretoria
1068. Union of South Africa, Department of Public Health (1931) *Annual Report*, Pretoria, p 54

Seychelles and Madagascar

1069. Cloitre, J (1930) *Bull Soc Path. exot.*, 23, 342

Turkey

1070 Akçay, S. (1955) *Vet. Fak Derg*, 2, 107
1071. Eser, S (1956) *İstanbul Üniv Tıp Fak Mec*, 19, 114
1072. Eser, S & Velicangil, S (1956) *İstanbul Üniv. Tıp Fak. Mec*, 19, 129
1073. Eser, S & Velicangil, S (1958) *Schweiz Z. allg Path.*, 21, 629
1074 *J Amer med Ass*, 1949, 140, 343
1075. Saka, O (1938) *Virchows Arch. path. Anat*, 302, 228

Lebanon

1076. Abu Haydar, N (1959) *J méd liban*, 12, No 2, p. 125
1077 Chaia, J. (1953) *Rev méd. Moyen-Orient*, 10, 488
1078 Chaia, J. (1953) *Sem Hôp. Paris*, 29, 154
1079 Ciaudo, D (1950) *Bull. Actual méd*, 3, 183
1080 Ciaudo, D et al (1948) *Sem Hôp Paris*, 24, 2502
1081 Refet, A. A. (1945) *Rev méd franç Moyen-Orient*, 3, 179

Israel

1082 Feldman, J D (1955) *Lab Invest.*, 4, 123

Indian peninsula

1083. Allen-Mersh, M. G (1945) *Indian med Gaz*, 80, 606
1084 Bajaj, N L (1940) *Indian med Gaz*, 75, 734
1085. Bodas, M. K. & Deshmukh, P. L. (1958) *J. Indian med Ass*, 31, 487
1086 Bramley, M J (1833) *Trans med phys. Soc. Calcutta*, 6, 181
1087. Chaudhri, J R (1929) *Indian med Gaz*, 64, 492
1088 Dunant, W (1950) *Maroc méd*, 29, 1148
1089 Dutt, B & Kebar, N D (1959) *Brit vet J.*, 115, 176
1090 Evans, G. M. (1944) *Nursing Mirror*, 11 November, p. 75
1091 Fayrer, J (1874) *Lancet*, 2, 580, 617
1092 French, C E. et al (1959) *J Nutr*, 68, Suppl No 2, p 63
1093 Government of India (1945) *Annual report of the Public Health Commissioner, Government of India*, Delhi, p 36
1094 Harrer, H. (1953) *Seven years in Tibet*, London, p 56
1095 Hettche, H. O (1956) *Arch. Hyg (Berl)*, 140, 79
1096. Indian Council for Medical Research (1957) *Technical report of the Scientific Advisory Board for the year 1957*, New Delhi, p. 230
1097. *Indian med Gaz*, 1941, 76, 95
1098. [illegible] 1959 171 1137
1099 [illegible]
1100. [illegible]
1101. [illegible]

1102. McCarrison, R. (1908) *Lancet*, 2, 1275
1103. McCarrison, R. (1913) *Lancet*, 1, 219 (See also ref. 9)
1104 McCarrison, R. (1915) *Indian J med. Res.*, 2, 778
1105 McCarrison, R. (1917) *The thyroid gland*, London
1106. McCarrison, R. (1924) *Brit. med. J.*, 1, 989
1107. McCarrison, R. (1927) *Brit med. J.*, 1, 94
1108. McCarrison, R. (1928) *The aetiology and epidemiology of endemic goitre.* In: *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p. 304
1109. McCarrison, R. & Madhava, K. B. (1932) *The life line of the thyroid gland*, Calcutta (Indian Medical Research Memoirs, No. 23)
1110. McCarrison, R. & Sankaran, G. (1931) *Indian J. med. Res.*, 19, 67
1111. McCarrison, R., Sankaran, G. & Madhava, K. B (1930-31) *Indian J med. Res.*, 18, 1335
1112. McCarrison, R. et al. (1927) *Indian J. med. Res*, 15, 207
1113 McClelland, J. (1835) *Some inquiries in the province of Kemaon, relative to geology, and other branches of natural science*, Calcutta
1114 McClelland, J. (1835) *Trans. med. phys. Soc. Calcutta*, 7, 145
1115 McClelland, J. (1859) *Sketch of the medical topography, or climate and soils, of Bengal and the N.W. Provinces*, London
1116. Macnamara, F N (1880) *Climate and medical topography in their relation to the disease-distribution of the Himalayan and Sub-Himalayan districts of British India with reasons for assigning a malarious origin to goitre and some other diseases*, London
1117. Megaw, J W D. & Gupta, J. C. (1927) *Indian med. Gaz.*, 62, 299
1118. Murray, M. M et al. (1958) *Trans. roy. Soc. trop Med. Hyg.*, 52, 223
1119 Ramalingaswami, V (1953) *Bull. Wld Hlth Org.*, 9, 275
1120. Ramalingaswami, V (1958) *Endemic goitre.* In: Trowell, H. C. & Jelliffe, D B., *Diseases of children in the subtropics and tropics*, London, pp. 200-206
1121 Raman, G & Beierwaltes, W H. (1959) *J. clin. Endocr.*, 19, 228
1122. Roychowdhury, S P & Gyani, B. P. (1958) *Indian J. appl Chem.*, 21, 41
1123 Seal, S. C. & Bhattacharji, L. M. (1957) *Report on a rapid medical and general health survey of the Sikkim State (1954)*, Calcutta, p. 71
1124 Sen Gupta, S R. & Swarup, S (1956) *Indian J. Pediat.*, 23, 162
1125 Sinclair, H M., ed. (1953) *The work of Sir Robert McCarrison*, London
1126 Sinha, R. V N., Bose, A. & Roychowdhury, S. P. (1959) *J. Indian med Ass*, 32, 325
1127. Stott, H (1932) *Indian J. med. Res.*, 20, 139, 147.
1128. Stott, H & Gupta, S P. (1934) *Indian J med. Res*, 21, 649, 655
1129 Stott, H et al (1930-31) *Indian J. med. Res.*, 18, 1059
1130. Watkin, D M et al (1959) *J. Nutr*, 68, Suppl. No. 2, p. 35.
1131. Wilson, D. C. (1941) *Lancet*, 1, 211

Ceylon

1132 Greenwald, I (1953) *Ceylon med. J.*, 2, 140
1133 Wilson, D. C. (1950) *Survey of endemic goitre in Ceylon* (Unpublished working document, WHO)
1134. Wilson, D C. (1954) *Brit J Nutr*, 8, 90

Burma

1135 Postmus, S (1956) *Proc. Nutr. Soc*, 15, 35
1136. Raymond, R. L. (1940) *Report on the goitre and general medical survey, Chin Hills, January to April 1940* (Unpublished)
1137. Seagrave, G. S (1954) *Int. Rec. Med. G P. Clin*, 167, 79

Thailand

1138 Klerks, J V (1959) *Final report on nutrition in Thailand* (Unpublished report, WHO)

1139 Ramalingaswami, V (1956) *Summary report on nutritional situation in Thailand* (Unpublished report, WHO)

1140 Van Eekelen, M (1957) *Voeding*, **18**, 336

Indo-China (Cambodia, Laos and Viet Nam)

1141 Billet, A (1896) *Deux ans dans le Haut-Tonkin (region de Cao-Bang)*, Lille, p 251

1142 Jeanselme, E (1910) *Rev Méd Hyg trop*, **7**, 317

1143 Leuret, J (1955) *Concours méd*, **77**, 4559

Malaya

1144 Le Mare, D W (1948) *Malay Nat J*, **3**, 70

1145. Pallister, R A (1940) *J Malaya Br Brit med Ass*, **4**, 191

1146 Polunin, I (1951) *Med J Malaya*, **5**, 302

Indonesia

1147. Bommel, L B van (1930) *Struma endemica en cretinismus in Nederlandsch-Indië, meer in het bijzonder in de Alaslanden*, Leiden (Thesis)

1148 Brenner, J F von (1894) *Besuch bei den Kannibalen Sumatras*, Würzburg

1149 De Haas, J H (1930) *Meded Dienst Volksgezondh Ned-Ind*, **19**, 191

1150 Donath, W F (1929) *Meded Dienst Volksgezondh Ned-Ind*, **18**, 402

1151 Eerland, L D (1932) *Geneesk T Ned-Ind*, **72**, 1299

1152 Eerland, L D (1934) *Geneesk T Ned-Ind*, **74**, 274

1153 ... *dlungsbericht*, ... , Bern, p 469

1154 ... *-Ind*, **75**, 184

1155

1156 Fraga de Azevedo, J, Franco Gândara, A & Pedroso Ferreira, A (1958) *An Inst Med trop (Lisboa)*, **15**, 189

1157 Gulik, P J van (1936) *Geneesk T Ned-Ind*, **76**, 541

1158 ... 42

1159

1160

1161

1162

1163

1164

1165

1166 Simons, L H (1933) *Een bijdrage tot de kennis van het endemisch kropgezwel en cretinisme in de Gajo- en Alaslanden*, Amsterdam (Thesis)

1167. Simons, L H (1939) *Geneesk T Ned-Ind*, **79**, 1418

1168

1169

1170

1171.

Borneo

1172 Clarke, M C (1951) *Trans roy Soc. trop Med Hyg*, **44**, 453

1173. Economic Advisory Council, Committee on Nutrition in the Colonial Empire (1939) *First report 2 Summary of information regarding nutrition in the Colonial Empire*, London, p 65

1174. Mazat, A O (1958) *J Amer med Ass*, 167, 2159
1175 Regester, P T (1956) *J roy Inst publ Hlth*, 19, 350

China (mainland)

1176 Adolph, W. H & Ch'en, S C (1930) *Chin J. Physiol*, 4, 437
1177 Adolph, W H & Tang, P S (1937) *Nutr. Notes (China)*, No 7, p 1
1178 Adolph, W H & Whang, P C (1932) *Chin J. Physiol*, 6, 345
1179 Bolt, R A (1914) *Chin. med J*, 28, 336
1180 Cheng, L T. & Ku, H C. (1939) *Contr. biol Lab Sci Soc. Chin, Zool Ser*, 13, 91
1181 *Chin J intern Med*, 1959, 7, 1151
1182 *Chin med J*, 1959, 79, 304
1183 Editorial Board, Chinese Journal of Internal Medicine (1959) *Chin med J*, 79, 219
1184 Galt, C M (1928) *Chin med J*, 42, 420
1185 Hewett, J W (1904) *Chin med J*, 18, 144
1186 Hosie, A (1897) *Three years in Western China*, 2nd ed, London, pp 49, 115-116
1187 Hosie, A (1914) *On the trail of the opium poppy*, London, vol 1, p 92, vol 2, pp 72, 78, 88-89, 93
1188. Ikeya, S (1938) *Beitr klin Chir*, 167, 441
1189. Ito, N (1938) *Mansyu Igaku Zassi*, 28, 529, 545, 557 (Abstract section, pp 46, 47, 48)
1190 King, G E (1919) *Chin med J*, 33, 38
1191 Kodama, T, Suzuki, S & Masayama, S (1935) *Mansyu Igaku Zassi*, 22, 103 (Abstract section, p 11)
1192 Kubo, H (1935) In *Transactions of the Ninth Congress of the Far Eastern Association of Tropical Medicine 1934*, Nanking, vol 2, p 481
1193 Lee, T (1941) *Chin med J*, 59, 379
1194 Lewis, S C (1909) *Chin med J*, 23, 173
1195 Liljestrand, S H (1933-34) *J W Chin Border Res Soc*, 6, 196
1196 Liu, J H & Chu, C K (1943) *Chin med J*, 61, 95
1197 McClendon, J F (1939) *Iodine and the incidence of goiter*, Minneapolis, pp 83, 90
1198 Maxwell, J L (1929) *The diseases of China*, 2nd ed, Shanghai
1199 Miller, H W (1928) *Chin. med J*, 42, 897
1200 Miller, H W (1929) *Chin med J*, 43, 226
1201 Miller, H W (1933) *Chin med J*, 47, 953
1202 Noda, K (1939) *Nippon Naibunpi Gakkai Zassi*, 14, 977
1203 Popovich, P P (1959) *Probl Endokr Gormonoter*, 5, No 4, p 105
1204 Robertson, R C (1939) *Lancet*, 2, 108
1205 Robertson, R C (1940) *China J*, 32, 26
1206 Robertson, R C (1941) *J clin Endocr*, 1, 285
1207 Rock, J F (1926) *Nat geogr Mag*, 50, 133
1208 Suzuki, S (1938) *Mansyu Igaku Zassi*, 28, 881 (Abstract section, p 67)
1209 Takamori, T (1938) *Jap J med Sci (8 Intern Med, Pediat & Psychiat)*, 4, 316*
1210 Takamori, T (1939) *Jap. J med Sci (8 Intern Med, Pediat & Psychiat)*, 5, 129*
1211 Takei, U [illegible]
1212 Takei, U [illegible]
1213 Takei, U [illegible]
1214 Thorp, J [illegible] Peking, pp [illegible]
1215 Warwick, A (1923) *Nat geogr Mag*, 43, 113

Korea

1216 *Bull Manila med Soc*, 1912, 4, 42
1217 Mills, R G (1911) *Chin med J*, 25, 277
1218 Smith, R K (1928) *Chin med J*, 42, 270
1219 Williams, R R et al (1959) *J Nutr*, 68, Suppl No 1

Taiwan

1220. Chen, T.-C. (1952) *Taiwan Igakkai Zassi*, 51, 469
1221. Chen, T -C. (1954) *Taiwan Igakkai Zassi*, 53, 593
1222. Chen, T -C (1955) *Taiwan Igakkai Zassi*, 54, 17
1223. Chen, T.-C. (1955) *Taiwan Igakkai Zassi*, 54, 180
1224. Chen, T.-C. (1956) *Taiwan Igakkai Zassi*, 55, 346
1225. Hashimoto, Y. & Kyo, K (1941) *Taiwan Igakkai Zassi*, 40, 914
1226. Hashimoto,Y. & Sha, S (1941) *Taiwan Igakkai Zassi*, 40, 1256
1227. Kawaishi, K. (1940) *Taiwan Igakkai Zassi*, 39, 1667
1228. Ko, Y.-C (1956) *Taiwan Igakkai Zassi*, 55, 356
1229. Ko, Y.-C. (1956) *Taiwan Igakkai Zassi*, 55, 359
1230. Ko, Y -C (1956) *Taiwan Igakkai Zassi*, 55, 369
1231. Ko, Y -C. (1956) *Taiwan Igakkai Zassi*, 55, 373
1232. Ko, Y -C (1956) *Taiwan Igakkai Zassi*, 55, 377
1233. Ko, Y.-C. (1958) *Taiwan Igakkai Zassi*, 57, 613
1234. Kobayashi, C (1941) *Taiwan Igakkai Zassi*, 40, 784
1235. Sai, K. (1941) *Taiwan Igakkai Zassi*, 40, 1391
1236. Usuda, S (1941) *Jap. J Cancer*, 35, 256

Japan

1237. Aizawa, F. (1953) *Sapporo med J.*, 4, 118
1238. Aschoff, L. (1925) *Virchows Arch. path Anat*, 254, 841
1239. Aschoff, L. (1937) *Munch med. Wschr*, 84, 841
1240. Fujii, K et al (1940) *Iwate med Coll J*, 4, 140
1241. Fujii, K. et al (1955) *Rural Medicine, Hokkaido District Edition*, 3, No 1, p 36
1242. Fujii, K et al. (1956) *Rural Medicine, Hokkaido District Edition*, 4, No 1, p. 71
1243. Greenwald, I. (1958) *Trop. geogr. Med (Amst)*, 10, 149
1244. Harada, M & Ogawa, M. (1952) *Sapporo med J.*, 3, 347
1245. Hashiba, T, Ogawa, M & Otsuka, R (1952) *Sapporo med J*, 3, 252
1246. Hichijo, K. (1953) *Folia endocr jap*, 29, 155
1247. Hichijo, K (1957) *Fifty-fourth Scientific Session of the Japanese Society of Internal Medicine, Tokyo, April 1957*, Tokyo, Symposium 1, p. 37
1248. Hichijo, K & Kotani, A. (1954) *Kitakanto med J*, 3, 199
1249. Hichijo, K & Kotani, A (1954) *Kitakanto med J*, 4, 107
1250. Hichijo, K. et al (1955) *Kitakanto med. J*, 5, 238
1251. Inoue, Z et al (1954) *Hokkaido J. med. Sci*, 29, 223
1252. Katsumata, K. & Murakami, S. (1933) *Nagoya J med Sci*, 7, 59
1253. Katsunuma, S, Murakami, S. & Katsumata, S (1930) *Aichi med Soc. J.*, 37, 1279
1254. Kawaishi, K. & Hashimoto, Y. (1941) *Ann. Surg.*, 113, 481
1255. Kondo, K. (1953) *Sapporo med J*, 4, 113
1256. Kotani, A (1954) *Kitakanto med. J.*, 4, 71
1257. Kotani, A. (1955) *Kitakanto med J.*, 5, 225
1258. McClendon, J F (1933) *J biol. Chem*, 102, 91
1259. McClendon, J. F (1933) *Münch. med Wschr.*, 80, 1039
1260. McClendon, J F. (1935) *Münch med. Wschr*, 82, 901
1261. McClendon, J. F (1939) *Iodine and the incidence of goiter*, Minneapolis, p 85
1262. McClendon, J F. (1946) *J clin Endocr.*, 6, 589
1263. Maeda, Y. et al. (1955) *Acta path jap*, 5, 169
1264. Miyake, T. et al. (1954) *Acta Sch med Gifu*, 1, 333; 2, 45, 215
1265. Miyake, T. et al (1955) *Acta Sch med Gifu*, 3, 52
1266. Miyake, T. et al. (1957) *Acta Sch. med. Gifu*, 5, 550
1267. Morikawa, H. et al. (1953) *Transactiones Societatis Pathologicae Japonicae, Editio Generalis*, 42, 48

1268. Morinaga, H. (1954) *Rep balneol Lab. Okayama Univ*, No 14, p 51
1269 Morobashi, Y. (1932-1933) *Clinics and Treatment*, 1, 513
1270 [illegible]
1271. [illegible]
1272 [illegible]
1273. [illegible]
1274. [illegible]
1275 [illegible]
1276. [illegible]
1277. [illegible]
1278 [illegible]
1279. [illegible]
1280 [illegible]
1281. [illegible]
1282. Takamori, O & Yūki, Y (1956) *Jap J vet Sci*, 18, 159
1283 Takamori, O & Yūki, Y. (1956) *Jap J. vet Sci*, 18, 165
1284 Takamori, O & Yūki, Y (1957) *Jap J vet Sci*, 19, 31
1285 Takata, H. (1958) *Nippon Yakurigaku Zassi*, 54, 225
1286 Takata, H (1958) *Nippon Yakurigaku Zassi*, 54, 230
1287 Takeda, K et al (1942) *Hokkaido med J*, 20, 129
1288. Takenaka, S [illegible] 462, p 801
1289 Takenaka, S [illegible] 484, p 657
1290 Tanabe, H et [illegible]
1291 Usubuchi, L [illegible]
1292 Watanabe, N et al (1956) *J. Nara med Ass.*, 7, 101

Philippines

1293 Duncan, L C (1905) *Amer Med*, 10, 861
1294. Erickson, H A (1938) *J. Philipp Is med Ass*, 18, 67
1295. Estrada, J, Nery, P. T & De Vera, L B (1948) *J Philipp. med Ass*, 24, 109
1296 Greenwald, I (1952) *Bull Hist Med*, 26, 263
1297 Hall, H A. (1933) *J Philipp Is med Ass*, 13, 77
1298 Joson, T (1926) *Rev filip Med*, 17, 172
1299 Lopez-Rizal, L & Padua, R G (1926) *J Philipp. Is med Ass.*, 6, 113
1300 Nichols, H J (1909) *Philipp J. Sci B*, 4, 279
1301 Recio, P M (1950) *Acta med philipp*, 6, 321
1302 Reyes, C (1928) *J Philipp Is. med Ass*, 8, 155

Oceania (general)

1303 Clements, F W (1954) *Bull Wld Hlth Org*, 10, 105
1304 Hercus, C E (1949) In Royal Society of New Zealand, *Report of the Sixth Science Congress, May 1947*, Wellington, N Z, p 311

New Guinea

1305 Clements, F W (1936) *Med J Aust*, 1, 451
1306 Department of External Territories, Australia (1950) *Report of the New Guinea Nutrition Survey expedition 1947*, Sydney
1307. McCullagh, S F (1959) *Papua N Guinea med J*, 3, 43
1308. Zwart, D. (1959) *T Diergeneesk*, 84, 550

Australia and Tasmania

1309. Bachelard, H S & Trikojus, V. M (1960) *Nature (Lond)*, 185, 80
1310 Clements, F W (1948) *Med J Aust*, 1, 637

1311 Clements, F W (1953) *Med J Aust*, **2**, 251
1312 Clements, F W (1954) *Med J Aust*, **2**, 894
1313 Clements, F. W (1955) *Med. J Aust*, **2**, 369
1314 Clements, F. W (1958) *Aust dent J*, **3**, 383
1315 Clements, F W (1958) *Med J Aust*, **2**, 823
1316 Clements, F. W & Wishart, J W (1956) *Metabolism*, **5**, 623
1317 Green, R J (1956) *J. Aust Inst agric Sci*, **22**, 40
1318 Gibson, E W & Poate, H R G (1949) *Med J. Aust*, **2**, 151
1319. Hipsley, E H (1950) *Endemic goitre prophylaxis* (Memorandum submitted to the *National Health and Medical Research Council of Australia, May 1950)*
1320 Hipsley, E H (1956) *Med J. Aust*, **1**, 532
1321 Jungfer, C C (1948) In· *Report of the National Health and Medical Research Council, Commonwealth of Australia, 26th session*, Sydney, p 21
1322. Morris, E S. (1923) *Annual report of the Department of Public Health of Tasmania for the year ended June 30, 1922*, Hobart
1323 Osmond, A & Clements, F W (1948) *Med J Aust*, **1**, 665, 753
1324 Pryde, A (1944) *Med J Aust*, **1**, 525
1325 Smith, K V (1957) *Med J. Aust*, **1**, 625
1326 Southcott, W H (1945) *Aust vet J*, **21**, 35
1327 Stuart, A E (1955) *Aust J exp Biol med Sci.*, **33**, 429
1328 Stuart, A E. (1955) *Med J Aust*, **1**, 920
1329 Summons, W (1927) *Med J Aust*, **2**, Suppl, p 59
1330 Sutton, H (1923) *Med J. Aust*, **1**, 253
1331 Sutton, H. (1927) *Med J Aust*, **2**, Suppl, p. 20
1332 Wyndham, N (1940) *Med J Aust*, **1**, 756

New Zealand

1333 Bell, T W (1890) *N Z med J*, **3**, 67, 129
1334 Best, E (1905) *J. Polynes. Soc*, **14**, 1
1335 Best, E (1924) *The Maori*, Wellington, N Z, vol. 2, p 49
1336 Caro, D B & Hall, C D. (1954) *N Z med J*, **53**, 523
1337 Colquhoun, D (1910) *N Z med J*, **8**, 17
1338 Cunningham, I J (1955) *N. Z J Agric*, **91**, 602
1339 Dayus, C V, Taylor, B A & Thompson, G A (1941) *N Z J Agric*, **63**, 387
1340. Department of Health, New Zealand (1949) *Annual report of the Director-General of Health, New Zealand*, Wellington, N Z, p 32
1341 Fitchett, F. et al (1934) *Aust N Z J. Surgery*, **3**, 318
1342 Greenwald, I (1957) *J Hist Med.*, **12**, 72
1343 Hacon, W G. (1889) *N Z med J*, **2**, 244
1344 Hercus, C E (1927) *Med J Aust*, **2**, Suppl, p 12
1345 Hercus, C E (1953) *Canad med Ass. J*, **68**, 531
1346 Hercus, C E (1957) *Aust Ann Med*, **6**, 5
1347. Hercus, C E & Aitken, H A A (1933) *J. Hyg (Lond)*, **33**, 55
1348 Hercus, C. E. & Baker, E S (1921) *N Z med. J*, **20**, 116
1349 Hercus, C. E., Benson, W N & Carter, C L. (1925) *J Hyg (Lond)*, **24**, 321
1350 Hercus, C. E, Benson, W N & Carter, C L. (1926) *J Hyg (Lond)*, **25**, 471
1351
1352.
1353.
1354.
1355.
1356.
1357.
1358.

1359 Shore, R A. & Andrew, R L (1929) *Goitre in school-children The incidence of goitre in school-children in relation to the amount of iodine in soil and water in certain districts of the North Island of New Zealand*, Wellington, N Z (New Zealand Departments of Health and Scientific and Industrial Research)

1360 Shore, R A & Andrew, R L (1934) *Bull Off int Hyg publ*, 26, 252

1361 Shore, R A & Andrew, R L (1934) *Goitre in school-children The incidence of goitre in school-children in relation to the amount of iodine in soil and water in certain districts of the North Island of New Zealand*, Wellington, N Z (New Zealand Department of Scientific and Industrial Research, and Department of Health, Bulletin No 45)

1362 Shore, R A & Andrew, R L (1935) *Bull Off int Hyg publ*, 27, 700

1363 Sinclair, D P & Andrews, E D (1954) *N Z vet J*, 2, 72

1364 Tolley, M A T (1951) In *Annual report of the Director-General of Health, New Zealand, for the year 1950-51*, Wellington, N Z, p 68

South Pacific and Hawaiian Islands

1365 Economic Advisory Council, Committee on Nutrition in the Colonial Empire (1939) *First report 2 Summary of information regarding nutrition in the Colonial Empire*, London, p 114

1366 Faine, S & Hercus, C E (1951) *Brit J Nutr*, 5, 327

1367 Freeman, G C (1950) *Hawaii med J*, 10, 27

1368 Henderson, F M & Krantz, H C (1947) *J Speech Dis*, 12, 263

1369 Simmons, J S (1944) *Global epidemiology*, Philadelphia

———

HEALTH SIGNIFICANCE OF ENDEMIC GOITRE AND RELATED CONDITIONS

F. W. CLEMENTS, M.D., D.P.H., D.T.M.*

NATURAL HISTORY OF ENDEMIC GOITRE IN AFFECTED PERSONS

The Enlargement Process

Age of onset

Goitre can occur at any age in a person living in an endemic area. In localities where the incidence is high it is not uncommon for babies to be borne with a goitre In other areas, where this does not occur, pre-school children may have a visible enlargement of the thyroid gland. The highest incidence of endemic goitre in most goitrous areas occurs in girls 12 to 18 years of age, and in boys 9 to 13 years of age. Where an enlargement of the thyroid does not occur before school age it is reasonable to assume that the supplies of iodide available in the particular locality are sufficient to meet the requirements of the child for a certain number of years after birth, but for a high percentage of children there comes a time when the needs of growth or of other physiological events—for example, the onset of puberty and the taking of vigorous exercise—create demands for the thyroidal hormone which cannot be satisfied with the limited amounts of iodide available, and compensatory enlargement of the thyroid gland follows

An interesting observation, that has not yet been satisfactorily explained, is that even in the most goitrous areas of the world not all people suffer from thyroid enlargement McCarrison [70] found only about 90% of the population of the Gilgit Valley in Kashmir affected, and he considered this one of the worst-affected areas in the world. In many other highly goitrous

* Senior Medical Officer in Charge, Social Paediatrics, The Institute of Child Health, University of Sydney, Australia

regions not more than 50% of the female adolescent and adult population have a goitre If a simple goitre does not appear during childhood or adolescence it is rare for it to make its first appearance in adult males, but it is not at all uncommon for this to happen to women during pregnancy or lactation Lawson Tait [114] was one of the first to recognize the "step-wise" enlargement of the gland in women with each succeeding pregnancy. When people, and especially children, move from a non-goitrous area to a goitrous place, a significant number will develop a goitre, some within six months of arrival,[47] others not for three or four years.[111]

It should be appreciated that sporadic goitres, indistinguishable clinically from those occurring in endemic areas, are found in up to 4% of pre-adolescent and adolescent girls in non-goitrous areas. Some writers consider this condition a physiological enlargement This is true in the sense that it represents an increased physiological demand for thyroidal hormone, but basically the enlargement is an expression of an inadequate supply of iodide in these children at the final stage of hormone synthesis In such girls there may be some constitutional factor which results in high iodide requirements.

The hyperplastic phase

The initial enlargement of the thyroid is the direct result of the relatively prolonged action of one of the components of the thyroid-stimulating hormone (TSH) of the anterior pituitary gland on the cells of the thyroid It is generally agreed that the increase in the amount of TSH in the blood is the outcome of a lower than normal concentration of thyroidal hormone in the peripheral blood acting upon a sensitive mechanism in either the pituitary gland or the hypothalamus [53] The low concentration of thyroidal hormone in the blood is due to insufficient iodide being available for the manufacture of the hormone

Clinically, this type of enlargement presents as a uniform soft swelling, usually involving most of the gland, although occasionally one lobe is more enlarged than the other The hyperplastic phase is of relatively short duration, and it is not often that the physician has an opportunity of examining the gland while the enlargement is actually in progress Once the hyperplasia has reached the stage when the iodide being trapped by the gland is equivalent to that trapped by a normal non-enlarged gland, the gland structure starts to change to a colloid goitre.

Histologically, the initial enlargement consists of hyperplasia of the cellular components of the acini. The normal rounded acini with their [illegible] storted by ingrowths and [illegible] y the outcome of intense [illegible] capacity of the gland to [illegible] The amount of stainable colloid is reduced by the cellular overgrowth. Klinck [60] has described the

microscopical appearance of the thyroid glands from 10 infants and children who had gross enlargement of the gland which interfered with breathing or caused death by suffocation These glands were apparently in the stage of acute hyperplasia Most of the follicles were obliterated, or slit-like The cells lining the follicles were columnar, tall, and closely packed together Subendothelial masses of hyperplastic thyroid cells were found in some cases. Klinck believed these changes to have been brought about by the action of a goitrogen

If the cause of the hyperplasia is removed, be it iodide deficiency or the action of a goitrogen, while the gland is in this phase it sometimes becomes smaller, and may even return to normal

The colloid goitre

This is the resting stage of the gland and is the condition of the goitre felt in most children with an endemic goitre Clinically, it is indistinguishable from the gland during the hyperplastic phase, being a uniform soft enlargement Histologically, the gland is a mixture of hyperplasia with the return of colloid to the acini The ratio of hyperplasia to colloid will vary through the full range. The colloid goitre resembles the normal gland except that the luminae of the acini are larger and the walls are reduced to a thin layer of flat cubicular cells In most glands there are projections of the cellular linings of the acini into the colloid, these are presumably the remnants of infoldings of the epithelium during the hyperplastic stage The total iodide content of colloid goitres approximates to that of normal glands, but the concentration of the iodide (measured in terms of dry gland) is significantly less than in the normal gland—0 1% instead of about 0 2%.[75]

Theoretically, once a balance has been established between the iodide demands for thyroxine synthesis and the supplies available at this particular stage in gland function, there should be little or no change in the size or histology of the thyroid—so long, at least, as the physiological status of the person remains unchanged In clinical experience, however, this seldom seems to happen Both the supplies of iodide at the site of synthesis of thyroxine and the demands for the hormone fluctuate, with the consequence that there are periodic bursts of hyperplasia, often in localized areas of the gland, hence the frequent occurrence, histologically, of hyperplasia adjoining areas of colloid in the same gland When supplies of iodide increase, or the physiological demands for the thyroidal hormone decline, portions of the gland undergo involution

Since the process of thyroid enlargement in the hyperplastic phase and the maintenance of the resting (colloid) phase are designed to meet the normal physiological needs of the body for thyroidal hormone, it follows that these stages, at least, of endemic goitre are associated with euthyroidism

Adults who move into a goitrous area from a non-goitrous region occasionally develop a colloid goitre for the first time. The sequelae are similar to those noted for endemic goitres arising in childhood.

Variations in Prevalence of Goitre in Children

By localities

The Study-Group on Endemic Goitre, convened by the World Health Organization in 1952,[120] suggested that the most convenient age-groups for the study of the prevalence of endemic goitre in a locality are the new-born, schoolchildren and service recruits. A number of surveys have been made in different parts of the world on schoolchildren and, although the standards used by the investigators may have differed, rendering strict comparison impossible, the figures do offer some idea of the variation in prevalence. A sample of the results of surveys which lend themselves to comparison is given in the table below. Unfortunately, the results of many surveys have not been recorded by age and sex.

VARIATIONS IN PREVALENCE OF VISIBLY ENLARGED THYROIDS IN THREE AGE-GROUPS IN DIFFERENT LOCALITIES

Age-group (years)	Prevalence (%)									
	A	B	C	D	E	F	G	H	I	J
					Males					
6-8	0.5	—	2.7	8.6*	3.9*	6.0	13.4	4.5	1.4	8.1
9-11	1.2	3.1	5.4	—	—	13.0	17.5	5.8	3.7	9.0
12-14	3.8	5.0	3.8	14.2**	9.3**	16.0	13.1	5.1	6.4	9.9
					Females					
6-8	1.8	—	8.7	10.2*	5.0*	6.5	17.0	5.4	3.1	9.6
9-11	4.9	5.2	13.6	—	—	19.5	25.2	10.0	8.5	12.6
12-14	13.0	14.6	12.0	18.2**	10.9**	21.4	41.7	19.5	20.8	16.7

A Cincinatti, Ohio, USA [83]
B Oregon, USA [83]
C. Tennessee, USA [79]
D El Salvador [11]
E Belgian Congo [12]
* Age-group 5-9 years

F New Zealand [41]
G Victoria, Australia [15]
H Canberra, Australia [15]
I Tasmania, 1949 [15]
J. Tasmania, 1954 [15]
** Age group 10-14 years

The sex difference is marked in most localities, and there is a wide range of prevalence. Localities A and B were surveyed by the same investigator, as were localities G, H, I, and J. The Gippsland District of Victoria (G) is an area of high endemicity compared with Cincinnati and Oregon.

Secular trends

Workers in widely separated parts of the world have reported an increase in the incidence of endemic goitre following the First and Second World Wars. Such an increase apparently occurred in Eastern Europe,[69] Western Europe,[4, 55, 58] England,[28] Taiwan,[14] and New Zealand.[99] In this connexion it is of interest to read in Hirsch's work [48] the records of epidemics of goitre in France at the end of the eighteenth and in the early part of the nineteenth century. Various explanations have been offered for these "epidemics", including changes in the food and water supply, and specific deficiency of iodine. No direct evidence has been brought forward in support of these various claims.

An annual epidemic of goitre in children attending three schools in Southern Tasmania has recently been studied.[37] It was noted that the same children appear to be affected each year, and these constituted some 30% of those studied. No differences were found in the physical environment, economic status, way of life, dietary pattern, or milk consumption of these children compared with those who had a normal thyroid gland throughout the period of study (boys, 18%; girls, 25%) and those who had a constantly enlarged thyroid (boys, 29%, girls, 22%)

The seasonal increase in size appears to coincide with the spring flush of pastures and weeds, and lends further support to the hypothesis advanced by Clements [18] that a food goitrogen present in the milk and originating in weeds or fodder is responsible for the epidemics There was some evidence that susceptibility to the food goitrogen may be an inherent characteristic of the children affected.

Sequelae of Colloid Goitre in Childhood

After introduction of prophylactic iodide

When increased amounts of iodide are given to children with an established endemic goitre, which is usually predominantly in the colloid phase, the gland frequently becomes smaller and, while remaining uniform in consistency, becomes firmer. In the author's experience a well-established goitre, in children living in an area where goitre has been shown by iodide prophylaxis to be due to iodide deficiency, does not usually disappear even with the prolonged administration of adequate amounts of additional iodide Similar results have been reported from southern Hungary, where only 16% of children with enlarged thyroids responded to iodide therapy.[115] However, Eugster [31] reports that "76 per cent of the people who moved to a goitre-free region lost their goitre after 20 years". The possibility that in some localities simple goitre may be due to the action of a goitrogen might explain this disappearance When the goitrogen ceases to operate

the gland becomes smaller. This was observed to happen with a number of drugs which had been prescribed for a variety of conditions and which were found to produce goitre The goitre disappeared on cessation of the therapy, this has been recorded for iodides,[7, 77, 101] resorcinol,[10] and thiocyanate [5, 92]

If a well-established goitre due to iodide deficiency is detected in a young child and adequate iodide prophylaxis is continued throughout the remainder of the growing period, the thyroid gland increases little in size compared with the over-all growth of the child, so that such children may reach adulthood without a visibly enlarged thyroid If the prophylaxis is continued throughout adult life, special attention being paid to the increased demands during pregnancy and lactation, it is unlikely that unfavourable sequelae will occur either in the thyroid gland, in the general health of the person, or in the growth, development or health of subsequent generations

The introduction of adequate prophylaxis in a goitrous area brings about a sharp fall in the incidence of goitre in children, as numerous workers have testified [16, 33, 46, 56, 78, 81, 100, 107] A careful study, made by the author over a number of years, of the child population of a city in a moderately severe goitrous area revealed that the drop in incidence was largely due to prevention of the development of goitres in children as they moved into the age-groups usually affected, and to the prevention of palpably enlarged thyroids from becoming visibly enlarged.

Effects of treatment with thyroid

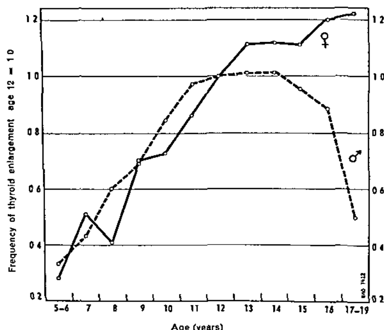
An interesting development, several years ago, was the re-discovery, by Greer & Astwood,[40] that the administration of thyroid preparations to children and adolescents brought about the disappearance of visible goitres As Greer & Astwood point out, this fact was established by numerous clinicians, mainly in Europe, in the 70's and 80's of the last century, and was then lost sight of for over 70 years A group of workers [51] in Czechoslovakia recently had a similar experience with thyroglobulin The wisdom of this form of treatment and prophylaxis could be questioned; the results are presumably achieved by suppression of the secretion of the TSH of the anterior pituitary by maintaining an adequate blood-level of thyroidal hormone from exogenous sources. One wonders how long this form of treatment could be continued without permanently affecting the capacity of the anterior pituitary to produce TSH.

In absence of treatment or prophylaxis

When additional iodide is not taken or treatment along lines similar to those indicated above is not given there is usually a progressive enlargement of the thyroid gland with advancing age through childhood. In many

localities with a high incidence, a marked increase in size occurs in girls in the pre-adolescent phase up to the menarche. These girls frequently exhibit an increase in thyroid size with each menstrual period for a few years. The progressive increase in size stops somewhere between 15 and 18 years of age. The author has not recorded a pre-adolescent spurt in goitre size in boys. Stocks [110] collected together the results of surveys made by a number of workers and related the prevalence of thyroid enlargement at various ages to the prevalence at the age of 12 years. These he compounded into a single set of figures for each sex His results are expressed graphically in the figure below

INCIDENCE OF THYROID ENLARGEMENT AT VARIOUS AGES, EXPRESSED IN TERMS OF FREQUENCY AT 12 YEARS OF AGE *



* Graph drawn from data compiled by Stocks [110]

It can be seen that there is a rise in the rate of thyroid enlargement up to 12 years of age in both sexes, and that this continues in the girls into early adult life However, in boys the rate commences to fall after 14 years of age, thus confirming the clinical impression that many youths lose their goitres in adolescence and early adult life.

From adolescence onwards a goitre behaves in one of the several ways indicated in the next section

Sequelae of Endemic Goitre in Adults

Development of a nodular goitre

The clinical experience of physicians in goitrous areas is that although simple goitres often disappear in adult males, it is not common for this to happen in adult females, particularly those who bear children. Regular, adequate iodide prophylaxis against endemic goitre is frequently difficult to maintain in many highly goitrous areas From the clinical histories and the appearance of the thyroid it would seem that goitres in women repeatedly go through periods of hyperplasia alternating with the resting phase, with subsequent involution leading to the formation of nodules within the gland substance.[93]

The nodules may be single or multiple; the latter are more often scattered irregularly throughout the gland tissue than distributed symmetrically Small nodules are not easy to detect clinically and frequently are only found at operation, biopsy or autopsy. Large nodules may produce pressure symptoms, especially those in the lower pole, which if on a pedicle may become a true intra-thoracic goitre.[94] Wegelin[117] found that nodules were rare in children under 10 years of age In a survey of some 22 000 school-children in Tasmania, I detected nodules in slightly less than 2% of the children between 9 and 15 years who had a visible goitre. Nodules become increasingly common after 15 years of age, and the prevalence of nodular goitres varies from one section of the population to another. Histologically, the repeated alternate hyperplasia and involution results in a marked increase in connective tissue in the stroma of the gland, and the arteries often show progressive endarteritis with a corresponding reduction in the supply of blood to the acini, which degenerate to colloid retention cysts; sometimes these cysts are of enormous size[104] The cells lining them are flattened to such an extent as to suggest that there could be very little or no activity

Macroscopically, the cut section of the thyroid often suggests that the nodule is encased in a fibrous capsule; this is not a true capsule, but merely the arrangement of the hypertrophied connective tissue, some of which is seen to contain remnants of glandular material

In some goitrous areas the processes of alternate hyperplasia and involution occur so frequently that the outcome is a very large nodular goitre hanging down on to the chest wall. These goitres often contain cysts, some of which, on section, are found to be haemorrhagic.

Persistence of a colloid or nodular goitre with euthyroidism

This is the usual sequel, at least in one phase of an endemic goitre. The only disadvantage is the aesthetic one Clinical experience, once again,

suggests that this is more likely to happen during the third and fourth decades of life, for in later life a significant number of people, especially women, suffer from mild degrees of myxoedema.[112]

Persistence of a colloid or nodular goitre with hypothyroidism

Many of the earlier textbooks claimed that, by definition, endemic goitre is always associated with euthyroidism. This is undoubtedly true of the uncomplicated endemic goitre during the hyperplastic and colloid phases, but once degenerative changes with the subsequent formation of nodules occur it is reasonable to argue that the condition is no longer endemic goitre. The progressive destruction of epithelial elements by the overgrowth of the stroma and the pressure of enlarging colloid spaces gradually reduce the capacity of the thyroid gland to produce thyroxine. Because the processes of hyperplasia and involution are more frequent in females than in males, often being associated with repeated pregnancies,[112] it is not surprising that myxoedema of this origin occurs much more frequently in women than in men; Osler[84] gives the relative proportions as about 6 : 1. This form of myxoedema, because of its slow onset, is difficult to detect. Since the development of this condition is generally postponed until the fifth or sixth decade, the accompanying reduction of physical and mental activity is often attributed to age by the patient and her friends. Physicians with long experience in goitrous areas are aware of these changes in many of their female patients with long-standing goitres.

Clinically, the signs and symptoms of myxoedema which arises in this way are not different from those described in textbooks; it is probable that much of the earlier descriptive material was drawn from patients with myxoedema of this origin.

Development of secondary thyrotoxicosis

Several writers have drawn attention to the possibility that endemic goitre predisposes to secondary toxic goitre. The evidence is indirect and, while it is not conclusive, it nevertheless strongly supports such a hypothesis. Campbell[13] compared the distribution maps for thyrotoxicosis and endemic goitre in the British Isles and concluded that "in the British Isles exophthalmic goitre is more likely to occur in connection with an area of endemic goitre." McClendon[71] showed that in North America the geographical distribution of thyrotoxicosis coincided with the areas of high incidence of endemic goitre. The same author worked out the number of cases of exophthalmic goitre per 100 cases of endemic goitre for various zones in Europe. This analysis failed to show a consistent relationship; for example, much higher figures for toxic goitre were obtained for certain parts of Northern Italy and Germany than for Switzerland, where the incidence of endemic goitre has always been considered to be very high. More recently,

Saxén & Saxén [97] have shown that the incidence of toxic goitre in Finland is considerably higher in the rural areas with a moderate or high incidence of simple goitre than in the rural areas with a low incidence of simple goitre. The approximate ratio of toxic goitre in the non-goitrous, moderately endemic and severely endemic areas was 1·2·3.5. In Australia, Wyndham [121] was the first to show that in the State of New South Wales "there seems to be, therefore, a natural tendency for these non-toxic goitres to become hyperplastic and hyperfunctional in middle life". Later Clements,[17] in an Australia-wide study, showed that the death-rates for thyrotoxicosis were highest in the states with the highest incidence of endemic goitre, and lowest in the states where endemic goitre does not occur. Reviewing some of this evidence, Rundle [94] concluded that "there is powerful evidence from goitre maps that endemic goitre predisposes to thyrotoxicosis". This conclusion seems justified for certain parts of the world, more particularly North America, the British Isles, and parts of continental Europe and Australia, *but the evidence in respect of other parts of Europe and many of the economically under-developed areas of the world is inconclusive or non-existent.* It is surprising that McCarrison [69, 70] and Stott and his co-workers [111, 112] failed to record toxic goitre in the highly goitrous valleys of the Himalayas and India In the high plateaux of the Andes, where several surveys have been made, there are only passing references to toxic goitre. Mahorner [73] was told that toxic symptoms do occur in the Indians of Guatemala who have large goitres, but apparently saw none himself in an extensive visit. Kimball [57] has made no reference in his survey of several Central and South American countries to the existence of toxic goitre, nor have Scrimshaw and his team in their various surveys in Central America.[11, 98] The one exception on the American continent is Mendoza Province, Argentina, where Perinetti [83] found a relatively high prevalence of toxicity superimposed on nodular goitre.

The irregular occurrence of thyrotoxicosis as a sequel of endemic goitre throughout the world raises two questions. Has the condition been overlooked in the localities where it has not been reported; and do the sequelae of endemic goitre differ in different localities? More intense, carefully controlled surveys will answer the first question. The answer to the second question may be bound up with the question of the etiology of endemic goitre.

Endemic goitre and carcinoma of the thyroid

The WHO Study-Group on Endemic Goitre [120] considered this subject briefly, reviewing the literature then available. The members of the Group were impressed with the suggestive character of the data, but felt that, at the time, it was not possible to form a firm opinion on whether endemic non-toxic goitre predisposes to carcinoma of the thyroid. Sokal,[103] after an extensive review of the American literature on endemic goitre, thyro-

toxicosis and carcinoma of the thyroid, came to the conclusion that thyroid cancer arises more frequently in toxic than in non-toxic goitre He set a figure of 1% expectancy of carcinoma during the lifetime of a patient with nodular goitre and further expressed the opinion that carcinoma was twenty times more common among persons with hyperthyroidism than among those with euthyroidism

More recently Miller,[76] after a review of patients at the Ford Hospital, Detroit, has expressed the opinion that Sokal's estimate that three-quarters of the cases of carcinoma arise in pre-existing nodular goitres is too generous In Miller's series only 6 out of 14 patients with non-papillary cancers gave a history of goitre of over one year's duration Saxén & Saxén [97] in Finland were unable to find any difference in the mortality rates for carcinoma of the thyroid between rural areas where endemic goitre was rare and those where it was moderately or highly prevalent Miller [76] has doubts whether this question can be solved with existing data.

Endemic goitre and carcinoma in general

Spencer [105, 106] has recently drawn attention to the possible influence of the thyroid in malignant disease. He found a correlation between the prevalence of endemic goitre and the number of deaths from malignant disease He points out that endemic goitre leads to hypothyroidism, with its accompanying reduced output of thyroidal hormone and, subsequently, lowered metabolic rate He quickly denies that these conditions should be considered a primary cause of cancer, he suggests rather that thyroid function or dysfunction may be associated with susceptibility or immunity to cancer He offers the hypothesis that hypofunction of the thyroid may be associated with premature senility of tissue cells, which in some way is associated with normal mitotic activity Ellerker [29] has demonstrated a clinical relationship between non-toxic goitre and malignant disease of the breast.

SEQUELAE IN PROGENY OF GOITROUS PARENTS

Cretinism

Endemic cretinism has been reported from a number of countries where endemic goitre occurs Before proceeding to discuss this, it is proposed to discuss cretinism in general

The derivation of the word "cretin" is unknown. A number of suggestions has been made from time to time that it is a distorted form of the French word *chrétien*—a Christian—meaning that those so called could not sin; that it came from the Latin *creta*, referring to the chalk-like, greyish-white faces of the victims, that it originated in the Rhaeto-Romanic

Saxén & Saxén [97] have shown that the incidence of toxic goitre in Finland is considerably higher in the rural areas with a moderate or high incidence of simple goitre than in the rural areas with a low incidence of simple goitre. The approximate ratio of toxic goitre in the non-goitrous, moderately endemic and severely endemic areas was 1:2.3.5. In Australia, Wyndham[121] was the first to show that in the State of New South Wales "there seems to be, therefore, a natural tendency for these non-toxic goitres to become hyperplastic and hyperfunctional in middle life". Later Clements,[17] in an Australia-wide study, showed that the death-rates for thyrotoxicosis were highest in the states with the highest incidence of endemic goitre, and lowest in the states where endemic goitre does not occur. Reviewing some of this evidence, Rundle [94] concluded that "there is powerful evidence from goitre maps that endemic goitre predisposes to thyrotoxicosis". This conclusion seems justified for certain parts of the world, more particularly North America, the British Isles, and parts of continental Europe and Australia, but the evidence in respect of other parts of Europe and many of the economically under-developed areas of the world is inconclusive or non-existent. It is surprising that McCarrison [69, 70] and Stott and his co-workers [111, 112] failed to record toxic goitre in the highly goitrous valleys of the Himalayas and India In the high plateaux of the Andes, where several surveys have been made, there are only passing references to toxic goitre. Mahorner [73] was told that toxic symptoms do occur in the Indians of Guatemala who have large goitres, but apparently saw none himself in an extensive visit. Kimball [57] has made no reference in his survey of several Central and South American countries to the existence of toxic goitre, nor have Scrimshaw and his team in their various surveys in Central America.[11,98] The one exception on the American continent is Mendoza Province, Argentina, where Perinetti [88] found a relatively high prevalence of toxicity superimposed on nodular goitre

The irregular occurrence of thyrotoxicosis as a sequel of endemic goitre throughout the world raises two questions: Has the condition been overlooked in the localities where it has not been reported; and do the sequelae of endemic goitre differ in different localities? More intense, carefully controlled surveys will answer the first question. The answer to the second question may be bound up with the question of the etiology of endemic goitre.

Endemic goitre and carcinoma of the thyroid

The WHO Study-Group on Endemic Goitre [120] considered this subject briefly, reviewing the literature then available The members of the Group were impressed with the suggestive character of the data, but felt that, at the time, it was not possible to form a firm opinion on whether endemic non-toxic goitre predisposes to carcinoma of the thyroid. Sokal,[103] after an extensive review of the American literature on endemic goitre, thyro-

tion of radioiodine in the neck. The hypothesis has been advanced by several writers[27, 72] that this condition arises as a result of failure of the thyroid "anlage" to develop from the oral portion of the mesobranchial arch

In a non-goitrous area this type of congenital cretinism predominates In a series of 60 cretins from the USA and Canada who were examined by Osler,[84] only seven had a goitre and three out of five children in one family were goitrous cretins (see next section). In their series of 115 cretins, Wilkins, Clayton & Berthrong[119] found six with goitres.

Cretins have been reported[101] with tumours in the neck which appeared to be enlarged thyroids As Benda[8] has pointed out, however, in most cases the tumour is probably a remnant of the fourth pharyngeal pouch The presence of any active thyroid tissue can be demonstrated by a test with radioactive iodine; if it is negative, the case can be classified as congenital thyroid aplasia

Congenital thyroid aplasia is seldom recognized at birth, although in retrospect it is possible to recall that many of the features characteristic of this condition were present then The baby is usually heavier than normal and has a large head with a wide-open anterior fontanelle and an open frontal suture. The limbs are short compared with the length of the trunk; the skin is greyish-white, dry, wrinkled and scaly, with loose folds about the wrists, hands and neck. The tongue is often protruding X-ray examination of the bones—and for this purpose the distal epiphysis of the femur and pelvis is most useful—shows delayed development of ossification centres In the skull, the cartilaginous disc between the clivus and the spheroid body is clearly to be seen Feeding such a baby is slow and tedious, and despite the amount of food eaten little or no weight is gained.

Throughout life physical growth is extremely slow, so that by the time adulthood is reached the true congenital thyroid aplastic is not more than 4 feet (1.2 m) long and, owing to the marked curvature of the spine, the standing height is seldom more than 3 feet (0 9 m). Many of the epiphysial centres remain open throughout adult life The nose is broad and flat and the thick puffy skin, especially around the eyes, gives the face a full apathetic appearance Dentition is delayed. So constant are these signs in persons with congenital thyroid aplasia throughout the world that a number of writers have suggested that they would appear to have belonged to one large family.

Parallel with the failure of physical growth there is an absence of mental development. The congenital thyroid aplastic remains an idiot, incapable of caring for himself Because there is no mental development, these people do not learn to speak and it is doubtful if they comprehend the spoken word, thus they are deaf-mutes They utter some harsh unintelligible sounds from time to time All movements are slow and awkward, and they walk with a shuffling unsteady gait.

language sometime in the sixteenth century and was applied to dwarfs;[8, 31, 45] that it is derived from the Latin *creatura*, meaning a creature, and came through the Romansh language of the Grisons, *creatura—cretira—cretin*[9] Whatever the precise origin of the word it was apparently used in a written document for the first time by Felix Platter,[89] in 1614, to describe a particular kind of person occurring in population groups in the valleys of the Alps in sufficient numbers to warrant identification[74] Platter noted the relatively wide distribution of cretinism, having read that it occurred in Egypt and having observed it himself in Carinthia and in his native Switzerland. The condition must have been common, for he reported that many children were affected.

His description covers the salient features: disproportion of the body (large head and short limbs, and immense tongue), deaf-mutism and mental retardation. He recognized that not all of these cretins had thyroid enlargement

European writers in the eighteenth and nineteenth centuries frequently drew attention to the co-existence in the same localities of endemic goitre and cretinism De Quervain,[25] however, recognized that in any group of so-called "cretins" there are likely to be a number of different types and that the signs displayed will depend upon the degree of active thyroid tissue present In his own words· "Le crétinisme endémique est loin de présenter toujours le même tableau Il y a d'abord des différences de degré."

Then, in 1871, Fagge[32] in England published accounts of another form of cretinism which occurred in people who had not, at any time in their lives, lived in a goitrous district. To this condition, Fagge gave the name "sporadic cretinism". In the 80 years since Fagge's observations a considerable number of studies have been made on cretinism. However, almost all of them have been on the sporadic form As a result of these investigations it is now possible to define a number of types of cretinism One classification based upon current knowledge is·

1 Congenital thyroid aplasia
2 Familial congenital goitrous cretinism.
3. Acquired athyroidism.
4. Acquired hypothyroidism.
5. Endemic cretinism.

Congenital thyroid aplasia

This condition is also known as congenital myxoedema[38] and congenital athyroidism. As the term implies, persons suffering from this condition are born without any functioning thyroid issue. Hamilton, Reilly & Eichorn[42] confirmed this when they showed that there was no accumula-

somal recessive gene Stanbury, who has identified and defined Group 4, has not ventured an opinion about the hereditary character of the defect but has reported that 3 out of 6 patients studied by him showed familial incidence of the disease. The possible significance of these developments in any consideration of the etiology of endemic cretinism is discussed later.

Acquired athyroidism and acquired hypothyroidism

As the names imply, these are variations in degree of the same condition. In the one there is complete failure of thyroid secretion, in the other there is partial failure leading to the development of a degree of myxoedema, hence the use of the term "juvenile myxoedema", which is sometimes applied to those so afflicted

A number of writers [21, 27, 28, 62, 85] claimed that the condition followed an infectious disease, for example, measles and whooping cough, in cases they had studied It is of interest that Fagge's original case occurred after an attack of measles with erysipelas [32] Other writers attribute the cause to birth injuries which extended to involve the thyroid gland A hypothesis advanced by McGirr & Hutchison [72] is that, in fact, some of these subjects possess enough thyroid tissue at birth to meet the needs up to that time and perhaps for some time after, but this later proves insufficient for the increased needs of the larger child.

It is obvious that the clinical appearance of children affected by either of these conditions will be influenced by the age of onset The older the child the less marked the effects, especially in respect of mental development and growth The amount of deficiency of thyroidal hormone will likewise affect the severity of the clinical signs.

Acquired athyroidism has most of the features of the congenital form Pale or yellow skin, thinning of the hair, coarseness of the skin, and arrested osteological development dating from the time of onset The hands often have a spade-like appearance Hearing and speech may be affected, depending upon the age of onset of the condition, and, in general, will bear a relationship to the degree of mental retardation The presenting features are usually failure to grow at a satisfactory rate and mental retardation

In the last few years attention has been drawn to two other types of acquired thyroid enlargement in infants and children Marked thyroid enlargement has been reported in a number of newborn infants whose mothers had taken one of the therapeutic antithyroid drugs during pregnancy [1, 22, 30, 38, 44, 50, 87, 95] Two infants, one of whom died shortly after birth, showed full cretinism, and a third displayed definite hypothyroidism The thyroid of the cretin who died showed much vascular enlargement, with marked hyperplasia of the glandular tissue; the acini, which were lined with low columnar epithelium, contained no colloid [50] The other cretin proved extremely difficult to feed—partly, perhaps, because of the large tongue—and failed to gain weight But a week after the condition had been

This form of cretinism is unmistakable and, as stated above, the descriptions have been built up from a detailed study of persons so afflicted living in non-goitrous areas One of the most interesting comments in this regard is that made by Osler,[91] that none of the cretins investigated by him came from the goitrous districts of Canada or the USA.

Infants and children with congenital thyroid aplasia respond to oral administration of dried thyroid gland or thyroxine. The results will depend upon the age of the child when the treatment is commenced and the thoroughness with which it is maintained

The recent report by Ainger & Kelly [3] of three siblings in a family with cretinism, two without thyroid enlargement and one with a small enlargement, whose parents were cousins, is of considerable interest. Examination of the genealogical background of this family revealed at least twelve additional closely related people who may have been similarly affected. This led the authors to suggest that in this family the cretinism was due to a specific inherited defect which, because of the history, was probably a Mendelian recessive factor

Familial goitrous cretinism

In the last 15 years or so a number of highly important observations have been made in the USA and Great Britain on a comparatively large number of goitrous cretins.[42, 67, 72, 102, 109] Intense biochemical studies on many of these people have enabled a classification of goitrous cretins based upon the specific defects in the metabolism of thyroxine to be developed [23, 52] On the basis of present knowledge, it would appear that there are at least four categories; further work may reveal more.

Group 1. These subjects lack the ability to oxidize iodide and form iodotyrosines, although the thyroid is able to concentrate iodide effectively.

Group 2 Members of this group can synthesize thyroid hormone, but cannot de-iodinate monoiodotyrosine and diiodotyrosine which are normally formed in the hormonogenic process.

Group 3. The members of this group lack the ability to couple iodotyrosines into iodothyronines (thyroxine).

Group 4 This group is characterized by abnormal iodinated polypeptides in the serum

Elaboration of the biochemical and clinical features of these various categories is outside the scope of this chapter The interested reader is referred to the original papers by Stanbury and his co-workers (see the chapter *Physiology of endemic goitre* on page 261 of this monograph and Stanbury & Querido [109]) and to the appropriate chapter in the book by Hsia [52]

From the point of view of endemic goitre and its sequelae, the real interest in this series lies in the familial character of the defects. Hsia has suggested that in categories 1 and 3 the defect is transmitted by an auto-

The following essential characteristics have been taken from the description given in the report of the Sardinian Cretinism Commission, published in 1848.[96] More recent accounts present an identical picture.[8, 26]

Even in the first half of the last century there was a general belief in cretinous districts that the cretinous infant exhibited appearances at birth which indicated its future fate. However, this belief was not held by everybody. Workers who have investigated sporadic goitrous cretinism, in recent times, recognize that many of these infants are apparently normal at birth and that the signs of cretinism do not appear until the middle of the first year, by which time the characteristic features of the cretin have made their appearance. At this age the fully developed cretin is retarded in physical growth and mental development. The head is large with wide fontanelles; there is a marked absence of any mental or bodily vivacity, and the infant spends long periods asleep The child does not walk until the sixth or seventh year, and speech is limited to a few harsh sounds. The lack of speech is a sequel to deafness, which is characteristic of the disease. The Sardinian Commission noted that there seemed to be no intermediate age between infancy and puberty, or between puberty and old age; infancy is prolonged to puberty, and old age succeeds at once. A fully developed cretin does not exceed 3 feet (1 m) in height The face bears the impress of stupidity The tongue is often large and protrudes between the teeth. This description applies to cretinism resulting from thyroid aplasia and is similar to that given for sporadic congenital thyroid aplasia

Other endemic cretins appear to have a small amount of functional thyroid tissue, at least during the early part of their life; this is sufficient to prevent the appearance of some of the features of the fully developed cretin Growth is not so stunted, such people often being more than 3 feet tall They frequently have some mental faculties and often limited speech.

Classification of endemic cretinism

The range of clinical signs seen in cretins in the old Kingdom of Sardinia prompted the Commission to define three types of cretin

1. Those with only vegetative faculties, entirely destitute of reproductive and intellectual powers and not capable of employing articulate language. These people were called "cretins"

2 Those endowed with vegetative and reproductive faculties and some of the rudiments of language The intellectual faculties of this type are strictly limited to expressing the bodily wants and are due solely to the impressions of the senses They were called "semi-cretins".

3. Those endowed with vegetative and reproductive faculties and possessed of a less imperfect language carried on by words and gestures. The intellectual faculties of this type are also less limited than those of the semi-cretins, but are always below the ordinary level Such people are, to

diagnosed and appropriate treatment commenced, it began to take its feeds normally and started to gain weight regularly. This continued as long as the thyroid medication was given.

Hypofunction and hyperplasia of the thyroid gland have occurred in a number of children who had been treated with cobalt for a blood dyscrasia, or whose mothers had been so treated during pregnancy. Klinck [60] reports severe effects, leading to death, in young infants whose mothers had been treated during pregnancy; in these cases the gland showed marked hyperplasia with almost complete obliteration of the follicles Kriss, Carnes & Gross [64] reported similar but less severe signs in a number of children, one of whom had severe myxoedema. Holly,[49] on the other hand, failed to detect any abnormal effects in 78 pregnant women or their progeny who were given cobalt and iron, or cobalt alone, for 80 days before delivery. Jaimet & Thode [54] found no evidence of thyroid enlargement or clinical hypothyroidism in 17 children given up to 6 mg of cobalt chloride per kg of body-weight per day for 10 weeks. Obviously a great deal more work needs to be done to clarify the position of cobalt as a goitrogen.

Other drugs, including iodide,[45, 77, 90] resorcinol,[10] thiocyanate,[5, 92] and perchlorate,[59] have been shown to produce hyperplasia of the thyroid in adults, sometimes with myxoedema. It is not proposed to elaborate further on these goitrogens. The list, which is not complete, is quoted to show the extensive range of drugs which have been found to produce goitre and hypothyroidism.

Endemic cretinism

Cretinism has been recognized in Europe as a clinical entity since the sixteenth century. It was not, however, until the end of the eighteenth century that Fodéré [34] published the first detailed scientific study. The recognition of cretinism in other parts of the world came considerably later.

At the present time endemic cretinism occurs in at least three regions of the world·

(*a*) in localized areas in the European Alps and in the plains of northern Italy; [28]

(*b*) in the foothills of the Himalayas and in isolated communities in the plains of the Indian peninsula, [69, 111, 112]

(*c*) in extremely isolated and restricted communities in the Belgian Congo.[12, 21]

There has been considerable confusion about certain aspects of endemic cretinism. In the main this arises from uncertainties of diagnosis and the arguments of at least two schools of thought about the etiology.

Description of endemic cretins

The diagnosis of fully established cretinism presents no difficulty Good descriptions have been given by numerous writers over the last 150 years

"myxoedematous" and "nervous" forms of cretinism must have materially influenced the figures for the prevalence of cretinism

Almost all writers on the subject of cretinism have recognized that some cretins have goitres while others do not. The Sardinian Commission[96] found that approximately one-third of the cretins investigated were without thyroid enlargements. In McCarrison's[69] series 56% were without goitres, while 60% of the 35 cretins studied by Stott & Gupta[112] in India had goitres

The presence of a goitre has not been used by any workers as a basis for classification, yet it would appear from the studies on sporadic cretinism that the athyroidic cretin and the goitrous cretin are different in their pathology. The former is born with a defect in the initial development of the gland, and the latter has some defect in the internal metabolism of the gland which prevents the formation of effective thyroidal hormone The athyroidic cretin cannot respond to increased amounts of TSH, while the goitrous cretin responds with hyperplasia and, later, fibrous degeneration of the tissue

Prevalence of endemic cretinism

In the previous section it was pointed out that the separation of non-cretinous idiots and simple mental defectives from true cretins and semi-cretins is difficult For this reason figures from surveys do not necessarily give an accurate picture of the extent of cretinism In general this is more likely to be true the older the records, although it has already been noted that Benda[8] considers that in the 1930's and 1940's many inmates of institutions for cretins were not cretins With these reservations it is difficult to interpret the figures from any survey

The Sardinian Commission discovered 7083 cretins in a population of 2 651 000 in the Sardinian States The rate varied from 0 01% to 2 79%, the latter obtaining in the Province of Aosta at the foot of Mont Blanc. The Commission assigned these cretins to the three categories it had defined, as follows

Confirmed cretins	2165
Semi-cretins . . .	3518
Cretinous persons	433
Unspecified	967

In other parts of Europe, during the nineteenth century, the prevalence varied considerably Many of the data are for military conscripts and do not relate to the whole population. The figures range from 4 to 22 per thousand The most affected regions were the Hautes-Alpes and Savoie, in France, and parts of southern Germany, Austria and Hungary It was noted that although the Hautes-Alpes and Savoie were so heavily affected, the Jura, in which there was a similar prevalence of goitres, had scarcely any cretinism (2 7 per thousand, including idiots)

some extent, capable of following an occupation and of carrying out manual labour. They were called "cretinous persons".

Nearly 100 years later De Quervain[25] employed practically the same classification. In addition, he recognized that the goitrous idiot and the goitrous mental defective in a goitrous community must be differentiated from the true cretin.

There is no doubt that many surveys made in European countries in the eighteenth and nineteenth centuries included idiots and other mental defectives in the records as cretins.[45] It is also fairly certain that numbers of idiots and mental defectives, who were not cretins, were admitted to institutions for cretins, when these were established in Europe, following Dr Guggenbuhl's example near Interlaken, Switzerland,[34] in the 1830's. Benda,[8] who comparatively recently worked for a number of years in Switzerland on endemic cretinism, and who visited areas of cretinism in Austria and France, made the following observation:

> Comparison of a large group of cretins in a Swiss institution or a Swiss community with a large group of feeble minded patients in an American institution for mental defectives would show that in the former group numerous patients are regarded as cretins whose equivalent and likeness can be found in the American institution where no cretinism exists.

There seem to be good reasons for assuming that a group of endemic "cretins" in European centres would include some mental defectives whose condition is probably not due to thyroid deficiency.

The clinical picture of cretinism, and so the classification of cretins, was further confused in the early part of this century by the writings of McCarrison[49] following his study of cretins in some of the Himalayan valleys. He described a form of "nervous cretinism", which he believed differed from the cretinism of Europe in that the subjects displayed bizarre posturing of the arms, often accompanied by a degree of rigidity and sometimes spasticity of the lower limbs. Many of these subjects had exaggerated reflexes. From his description it is almost certain that some of the cretins he observed had spastic paralysis of the lower limbs.

These observations by McCarrison were taken up by a number of European writers,[20, 63, 64] who subsequently described a condition which some called "thyroneural dystrophy". A number of these cases were presented to learned societies about 40 years ago and the discussions which followed most of these presentations showed that the majority of the audience rejected the need for a separate classification. These speakers, although admitting that it was unusual to find cretinism associated with injury at birth or other causes of diplegia, saw nothing extraordinary in this. In this connexion it is of interest to note that McCarrison reported that 14% of his cretins had had "difficult births".

Confusion about the diagnosis of the minor grades of cretinism, the separation of idiots and mental defectives, and the attempts to define

"myxoedematous" and "nervous" forms of cretinism must have materially influenced the figures for the prevalence of cretinism

Almost all writers on the subject of cretinism have recognized that some cretins have goitres while others do not The Sardinian Commission [96] found that approximately one-third of the cretins investigated were without thyroid enlargements. In McCarrison's [69] series 56% were without goitres, while 60% of the 35 cretins studied by Stott & Gupta [112] in India had goitres

The presence of a goitre has not been used by any workers as a basis for classification, yet it would appear from the studies on sporadic cretinism that the athyroidic cretin and the goitrous cretin are different in their pathology. The former is born with a defect in the initial development of the gland, and the latter has some defect in the internal metabolism of the gland which prevents the formation of effective thyroidal hormone. The athyroidic cretin cannot respond to increased amounts of TSH, while the goitrous cretin responds with hyperplasia and, later, fibrous degeneration of the tissue.

Prevalence of endemic cretinism

In the previous section it was pointed out that the separation of non-cretinous idiots and simple mental defectives from true cretins and semi-cretins is difficult For this reason figures from surveys do not necessarily give an accurate picture of the extent of cretinism In general this is more likely to be true the older the records, although it has already been noted that Benda [8] considers that in the 1930's and 1940's many inmates of institutions for cretins were not cretins With these reservations it is difficult to interpret the figures from any survey

The Sardinian Commission discovered 7083 cretins in a population of 2 651 000 in the Sardinian States The rate varied from 0 01% to 2 79%, the latter obtaining in the Province of Aosta at the foot of Mont Blanc The Commission assigned these cretins to the three categories it had defined, as follows

Confirmed cretins	2165
Semi-cretins	3518
Cretinous persons	433
Unspecified	967

In other parts of Europe, during the nineteenth century, the prevalence varied considerably Many of the data are for military conscripts and do not relate to the whole population The figures range from 4 to 22 per thousand The most affected regions were the Hautes-Alpes and Savoie, in France, and parts of southern Germany, Austria and Hungary. It was noted that although the Hautes-Alpes and Savoie were so heavily affected, the Jura, in which there was a similar prevalence of goitres, had scarcely any cretinism (2 7 per thousand, including idiots).

some extent, capable of following an occupation and of carrying out manual labour They were called "cretinous persons".

Nearly 100 years later De Quervain[25] employed practically the same classification In addition, he recognized that the goitrous idiot and the goitrous mental defective in a goitrous community must be differentiated from the true cretin.

There is no doubt that many surveys made in European countries in the eighteenth and nineteenth centuries included idiots and other mental defectives in the records as cretins[45] It is also fairly certain that numbers of idiots and mental defectives, who were not cretins, were admitted to institutions for cretins, when these were established in Europe, following Dr Guggenbuhl's example near Interlaken, Switzerland,[35] in the 1830's. Benda,[8] who comparatively recently worked for a number of years in Switzerland on endemic cretinism, and who visited areas of cretinism in Austria and France, made the following observation

> Comparison of a large group of cretins in a Swiss institution or a Swiss community with a large group of feeble minded patients in an American institution for mental defectives would show that in the former group numerous patients are regarded as cretins whose equivalent and likeness can be found in the American institution where no cretinism exists

There seem to be good reasons for assuming that a group of endemic "cretins" in European centres would include some mental defectives whose condition is probably not due to thyroid deficiency.

The clinical picture of cretinism, and so the classification of cretins, was further confused in the early part of this century by the writings of McCarrison[69] following his study of cretins in some of the Himalayan valleys He described a form of "nervous cretinism", which he believed differed from the cretinism of Europe in that the subjects displayed bizarre posturing of the arms, often accompanied by a degree of rigidity and sometimes spasticity of the lower limbs Many of these subjects had exaggerated reflexes From his description it is almost certain that some of the cretins he observed had spastic paralysis of the lower limbs

These observations by McCarrison were taken up by a number of European writers,[20, 83, 86] who subsequently described a condition which some called "thyroneural dystrophy". A number of these cases were presented to learned societies about 40 years ago and the discussions which followed most of these presentations showed that the majority of the audience rejected the need for a separate classification. These speakers, although admitting that it was unusual to find cretinism associated with injury at birth or other causes of diplegia, saw nothing extraordinary in this. In this connexion it is of interest to note that McCarrison reported that 14% of his cretins had had "difficult births".

Confusion about the diagnosis of the minor grades of cretinism, the separation of idiots and mental defectives, and the attempts to define

sized this point and explained the absence of cretinism from some goitrous valleys of the Himalayas by pointing out that goitre had made a relatively recent appearance in these regions.

There are a number of facts which do not support this hypothesis, some of which were put forward by the Sardinian Commission [96] and by even earlier writers [2]

(a) All writers admit that endemic cretinism does not occur in all localities in an endemic goitre area, even the suggestion that severe endemic goitre must have existed for several generations before cretinism occurs is not an adequate explanation for the difference Some regions such as the Jura have just as long a history of endemic goitre, with just as great an incidence, as the Hautes-Alpes and yet endemic cretinism has not been reported from the former region.[49]

(b) Cretinism is rare, if it occurs at all, in the Andes, where goitre has existed for several centuries

(c) Cretinism is often concentrated in villages and even in households in a village.[31, 69]

(d) Cretinism was more frequently met with the further investigators penetrated into the mountains of Hungary [43]

(e) Many cretins are the progeny of parents who did not have a thyroid enlargement. This was so in at least 4% of McCarrison's series, and the rate appears to have been much higher in some of the European studies [69, 98, 112]

(f) The prevalence of cretinism seems to bear a direct relationship to the extent of intermarriage within the cretinous districts [69, 96] It tends to disappear from those districts when one marriage partner comes from outside the district. Intermarriage has been extremely common in some of the remote, relatively land-locked valleys where cretinism has been most common With the development of communications more partners have come from outside these circumscribed localities The same could hold for pockets of land isolated by river systems, as in parts of India

This last observation, coupled with the studies on sporadic goitrous cretinism which have shown a high familial factor in the etiology, suggesting that it is due to a recessive Mendelian factor, raises the question whether much of the endemic goitrous cretinism has not the same etiology.

One argument that has been used to refute this possibility is discordancy among monozygotic t[illegible] f cretinism Eugster [31] collected from the literature [illegible] , six of whom were concordant in re[illegible] scordant. In a series of 15 non-[illegible]ive discordant Dissimilarity of [illegible]dence of the non-genetic [illegible]ark [116] have discussed [illegible]f monozygotic twins [illegible] have shown that

More recent surveys have shown much less cretinism in all the affected regions Eugster [31] records a cretin-rate ranging from 0 6% to 1.0%, with one Swiss village having a rate of 3.5%. However, even these figures do not relate to the current position Benda [8] states that the number of cretins in Switzerland is about 1 25 per thousand, spread over the whole country. It seems that one of the most recent surveys, limited to a circumscribed area, was made by Koller,[61] but even this is nearly 50 years old. He found 2% of the people in the Canton of Appenzell affected with cretinism, including all forms of mental retardation.

Benda has remarked on these relatively low figures, pointing out that the prevalence of mental deficiency in any population is around 2%. The obvious explanation is that the figures usually quoted relate to relatively large groups—for example, a canton or province—when, in fact, cretinism is limited to villages whose total population is a small percentage of the whole canton.

A surprising announcement on the prevalence of cretinism in Switzerland was made recently by Wegelin [119] He reported that cretinism had disappeared from Switzerland, presumably he meant that cretins were no longer being born there.

The last reports from the Himalayan and Indian foci are now 20 years old and neither McCarrison in his early surveys [69] (first decade of this century) nor Stott and his collaborators in the 1930's [111, 112] actually made a census. There certainly is need for a careful survey to determine the present position. Calonne [13] reported 4.3% of the entire population of the locality he studied in Ruanda-Urundi as being cretins. Benda [8] has suggested that any team investigating endemic cretinism should include a psychiatrist to help separate the non-cretinous mental defectives.

Etiology

The etiology has been deferred to the end because so little is known about it and because it has been the subject of marked controversy almost since cretinism was first studied. Writers on the etiology are divided on the relationship of endemic cretinism to endemic goitre Most writers favour a close causal relationship, pointing out that endemic cretinism is found only where there is endemic goitre. It is hard to interpret this statement when it is realized that up to two-thirds of all cretins have goitre No one has recorded whether goitrous cretinism exists in any locality where there is no endemic goitre in fully grown normal individuals. Those who hold the view that there is a causal relationship advance the hypothesis that the forbears of a cretinous child must have suffered from some enlargement of the thyroid gland through a number of generations, and that in each succeeding generation there is a progressive deterioration of the thyroid gland with the enlargement, leading to reduced function or dysfunction, until ultimately a cretinous child is born. McCarrison [69] empha-

sized this point and explained the absence of cretinism from some goitrous valleys of the Himalayas by pointing out that goitre had made a relatively recent appearance in these regions

There are a number of facts which do not support this hypothesis, some of which were put forward by the Sardinian Commission [96] and by even earlier writers.[2]

(a) All writers admit that endemic cretinism does not occur in all localities in an endemic goitre area; even the suggestion that severe endemic goitre must have existed for several generations before cretinism occurs is not an adequate explanation for the difference. Some regions such as the Jura have just as long a history of endemic goitre, with just as great an incidence, as the Hautes-Alpes and yet endemic cretinism has not been reported from the former region.[48]

(b) Cretinism is rare, if it occurs at all, in the Andes, where goitre has existed for several centuries

(c) Cretinism is often concentrated in villages and even in households in a village.[31, 69]

(d) Cretinism was more frequently met with the further investigators penetrated into the mountains of Hungary [48]

(e) Many cretins are the progeny of parents who did not have a thyroid enlargement This was so in at least 4% of McCarrison's series, and the rate appears to have been much higher in some of the European studies.[69, 96, 112]

(f) The prevalence of cretinism seems to bear a direct relationship to the extent of intermarriage within the cretinous districts [69, 96] It tends to disappear from those districts when one marriage partner comes from outside the district. Intermarriage has been extremely common in some of the remote, relatively land-locked valleys where cretinism has been most common With the development of communications more partners have come from outside these circumscribed localities. The same could hold for pockets of land isolated by river systems, as in parts of India

This last observation, coupled with the studies on sporadic goitrous cretinism which have shown a high familial factor in the etiology, suggesting that it is due to a recessive Mendelian factor, raises the question whether much of the endemic goitrous cretinism has not the same etiology

One argument that has been used to refute this possibility is discordancy among monozygotic twins in respect of cretinism Eugster [31] collected from the literature nine sets of identical twins, six of whom were concordant in relation to the cretinoid state and three discordant. In a series of 15 non-identical twins, 10 were concordant and five discordant Dissimilarity of monozygotic twins was once accepted as evidence of the non-genetic character of a disease or condition. Warkany & Selkirk [116] have discussed the appearance of hypothyroidism in one of a pair of monozygotic twins. They point out that extensive recent studies on twinning have shown that

the development of monozygotic twins can be severely modified by parental or post-natal non-genetic factors This would explain the appearance of cretinism in only one monozygotic twin, whereas the cretinous twins in the nine monozygotic sets collected by Eugster could all be genetic in origin

Recently, Raman & Beierwaltes[91] studied the serum-protein-bound iodine and the butanol-insoluble serum iodine in a group of people from a village in north-eastern India where there was a high incidence of endemic goitre, deafness, deaf-mutism, mental deficiency and cretinism Although they found lower mean figures for these components than those obtained in the USA, they were apparently unable to show any interrelationship between the various clinical conditions, nor has their work to date added further to our understanding of the etiology of endemic cretinism

Hitherto, the most widely held explanation for the manner in which endemic goitre produces cretinism in the progeny is that of thyroid degeneration or dysfunction associated with a goitre through repeated generations; however, this theory bears too much resemblance to Lamarckism and the inheritance of acquired characteristics to be accepted today. This fact, together with the strong suggestions of consanguinity in the parents of cretins, calls for an intense investigation of endemic cretinism where it still occurs, the use of modern techniques with radioactive iodide being combined with a thorough genetic study Recently, an exchange of correspondence on the origin of endemic cretinism has appeared in the medical press, but this has not succeeded in shedding any further light on the question.[19, 109] An unequivocal answer is all the more necessary because of the repeated statements in textbooks[53] and scientific articles[57, 98] that endemic goitre predisposes to endemic cretinism; it seems that such statements are often copied from one authority by another without any cognizance being taken of recent developments in genetics or in the study of sporadic cretinism.

Deaf-mutism

Deaf-mutism is one of the cardinal features of the fully developed cretin. This has led some workers to regard deaf-mutism alone, especially when it occurs in a goitrous locality, as being a sequel of endemic goitre, just as endemic cretinism has been assumed to be

During the last 40 years the etiology of many forms of deaf-mutism has been investigated While these studies have covered most countries in Europe and America, the most significant contributions have come from Switzerland, where it is estimated that 0.12% of the population are deaf-mutes[4, 43] It has been shown that about 40% of the deaf-mutism in Switzerland is inherited, of the remaining "sporadic" cases, an undisclosed number are true cretins and the others appear to have a congenital or acquired form of the disease. From their studies of the

genealogical trees of a large number of families with a history of deaf-mutism extending back for several centuries, Albrecht[4] and Hanhart[43] concluded that inherited deaf-mutism is due to a Mendelian recessive factor. Their evidence shows that the gene remains unimpaired for many generations, ready to reappear whenever it meets a similar gene.

The work of Gregg,[41] Swan et al.,[113] Patrick[86] and others in the 1940's demonstrated that maternal rubella, if it occurs during the first trimester of pregnancy, may lead to congenital deaf-mutism in the child Lancaster[65] has pointed out that rubella in populous areas was formerly almost entirely a disease of childhood. If a country or an area is isolated for any length of time rubella may die out and then, when re-imported, may attack individuals of all ages Under these circumstances it could well be that some cases of deaf-mutism in the population of isolated mountain valleys where endemic goitre occurs are a sequel of maternal rubella

The recognition of two forms of deaf-mutism which occur mainly as the result of the isolation of the population, and the complete absence of any biological explanation of how endemic goitre in parents can produce simple deaf-mutism in the offspring, calls for a review of the belief that one of the sequelae of endemic goitre is uncomplicated deaf-mutism.

Mental Deficiency

Mental deficiency without the other stigmata of cretinism has sometimes been considered to be a sequel of endemic goitre Most of those who have made this claim have not had close association with endemic cretinism[57, 98] The inclusion of mental defectives of normal height along with true cretins and semi-cretins in European institutions has undoubtedly added to this confusion[8] Extensive investigations of mental defectives in non-goitrous areas have failed to show any connexion between thyroid function and mental deficiency, except in relation to cretinism[80] There seems to be no justification for the statement that one of the sequelae of endemic goitre in the progeny is uncomplicated mental deficiency It is possible that the study of Raman & Beierwaltes[91] already referred to will, when completed, throw light on this problem also.

Conclusion

In the last section of this chapter doubts have been cast on the possibility that persons suffering from endemic goitre are more likely to produce cretins, deaf-mutes and mental defectives than persons living in a goitre-free locality

Recent research into sporadic cretinism has shown the need for an intensive investigation into endemic cretinism, using the same methods and techniques as have been used for sporadic cretinism

The discoveries in respect of inherited deafness and congenital deafness, the sequel of maternal rubella, have clearly revealed the need for making careful inquiries into the family history of persons with deaf-mutism alone in goitrous areas before labelling them the victims of endemic goitre.

REFERENCES

1. Aaron, H. H , Schneierson, S J & Siegel, E. (1955) *J. Amer. med Ass*, 159, 848
2. Ackermann (1790) *Über die Kretinen, eine besondere Menschenabart in den Alpen*, Gotha (Quoted by De Quervain & Wegelin [26])
3. Ainger, L. E. & Kelly, F. C (1955) *J clin Endocr.*, 15, 469
4. Albrecht, W (1934) *Z Hals-, Nasen- u Ohrenheilk.*, 36, 262
5. Barker, M H (1946) *Tex. St J. Med*, 42, 462
6. Bastenie, P. A. (1947) *Lancet*, 1, 789
7. Bell, G. O (1952) *Trans Amer. Ass Goiter*, p. 28
8. Benda, C E (1947) *Mongolism and cretinism*, London
9. Blackie, G. S (1855) *Cretins and cretinism*, Edinburgh
10. Bull, G M. & Frazer, R. (1950) *Lancet*, 1, 851
11. Cabezas, A , Pineda, T & Scrimshaw, N S (1953) *Amer J. publ Hlth*, 43, 265
12. Calonne, R (1939) *Ann Soc belge Méd. trop*, 19, 143
13. Campbell, J M H (1924-25) *Quart. J Med*, 18, 191
14. Chen, T (1952) *J Formosan med. Ass*, 51, 469
15. Clements, F W (1948) *Med J Aust*, 1, 637
16. Clements, F. W. (1953) *Med J. Aust*, 2, 251
17. Clements, F W (1954) *Med J. Aust*, 2, 894
18. Clements, F W (1956) *Metabolism*, 6, 623
19. Costa, A. (1957) *J clin Endocr*, 17, 801
20. Crookshank, F G (1913) *Proc. roy Soc Med (Sect. Dis. Child)*, 7, 26
21. Crotti, A (1935) *Diseases of the thyroid, parathyroids and thymus*, 3rd ed , Philadelphia
22. Davis, L J. & Forbes, W. (1945) *Lancet*, 2, 740
23. De Groot, L J & Stanbury, J. B. (1959) *Amer J. Med*, 27, 525
24. Demaeyer, E M. & Vanderborght, H. L. (1953) *Ann. Soc belge Med. trop*, 33, 579
25. De Quervain, F. (1924) *Schweiz Arch. Neurol Psychiat*, 14, 3
26. De Quervain, F. & Wegelin, C. (1936) *Der endemische Kretinismus*, Berlin & Wien
27. Dorff, G B (1934) *Amer J. Dis. Child*, 48, 1316
28. Eason, J. (1939) *Brit Med. J.*, 1, 1303
29. Ellerker, A G. (1955) *Proc. roy Soc. Med*, 48, 554
30. Elphinstone, N (1953) *Lancet*, 1, 1281
31. Eugster, J (1938) In. *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, Washington, p 131
32. Fagge, G H (1871) *Med-chir Trans*, 54, 155
33. Flaxén, W (1935) *Acta paediat. (Uppsala)*, 17, 565

... le goitre et le crétinage Turin

cr, 7, 47
J. Aust. (in press)
ational Goiter Conference
Washington, p 114
33

40. Greer, M A & Astwood, E. B (1953) *J clin. Endocr*, 13, 1312
41 Gregg, N McA. (1945) *Med J Aust*, 2, 122
42 Hamilton, J G, Reilly, W A. & Eichorn, K. B (1943) *Amer. J Dis Child*, 66, 495
43 Hanhart, E. (1938) *Z menschl Vererb - u. KonstitLehre*, 21, 609
44. Hepner, W R, jr (1952) *Amer. J. Obstet. Gynec*, 63, 863
45. Herbert, E M & Petrie, E (1954) *Lancet*, 1, 108
46 Hercus, C. E. (1953) *Canad med Ass. J*, 68, 531
47. Hercus, C E. & Baker, E S (1921) *N.Z. med J.*, 20, 116
48 Hirsch, A (1885) *Handbook of geographical and historical pathology*, London, vol. 2, p 121
49. Holly, R. G (1955) *J. Amer med. Ass*, 158, 1349
50 Hone, G M & Magarey, I (1948) *Med J Aust*, 2, 524
51 Hostomská et al (1954) *Čas Lék čes*, 93, 1064
52 Hsia, D Y. (1959) *Inborn errors of metabolism*, Chicago, p 156
53 Hubble, D & Hutchison, J H (1954) *Diseases of the thyroid gland and thymus*. In: Gaisford, W & Lightwood, R, ed, *Paediatrics for the practitioner*, London, vol 2, p 36
54 Jaimet, C H. & Thode, H C. (1955) *J. Amer. med Ass*, 158, 1353
55. Kaplan, M & Ducas, P. (1950) *Pediatrie*, 5, 191
56. Kimball, O P (1946) *J. Amer med. Ass*, 130, 1709
57. Kimball, O. P (1953) *Ohio St. med J*, 49, 313
58 *Kinderarztl Prax*, 1948, 16, 373
59 Kleinsong, H & Kruskemper, H. L. (1955) *Arch exp Path Pharmak*, 225, 172
60 Klinck, G. H (1955) *J Amer. med Ass*, 158, 1347
61 Koller, A (1911) (Quoted by Benda [9])
62 Kraus, W. M (1929) *Amer J med Sci.* 178, 315
63 Kraus, W M, Brock, S & Sloane, P (1929) [illegible] 178, [illegible]
64 Kriss, J [illegible] 117
65 Lancaste[illegible]
66 Langme[illegible]
67 Lerman, J, Jones, H W & Calkins, E (1946) *Ann intern. Med*, 25, 677
68. Ligdas, E (1953) *Dtsch. GesundhWes*, 8, 1025
69 McCarrison, R (1908) *Lancet*, 2, 1275
70 McCarrison, R (1915) *Indian J med Res*, 2, 778
71 McClendon, J. F. (1939) [illegible]
72 [illegible]
73 [illegible]
74 [illegible]
75 Marine, D & Lenhart, C H (1909) *Arch. intern Med*, 3, 66, 4, 440
76 Miller, J. M (1955) *New Engl J Med*, 252, 247
77 Morgans, M E & Trotter, W R. (1953) *Lancet*, 2, 1335
78 Muggia, G (1928) *La profilassi del gozzo endemico* In *Comptes rendus de la Conference internationale du goitre, Berne, 24-26 août 1927*, Berne, p 486
79 Mustard, H S. & Waring, J I (1927) *J Amer. med Ass*, 88, 714
80 Naville, F (1923) *Schweiz Arch. Neurol Psychiat*, 4, 67
81 Nicod, J L (1953) *Bull Wld Hlth Org*, 9, 259
82. Olesen, R (1924) *Publ Hlth Rep (Wash)*, 39, 1777
83 Olesen, R (1927) [illegible] 42, 1355
84 [illegible]
85 [illegible]
86 [illegible] (1948) *Med J Aust*, 1, 421
87 Pearlman, L N. (1954) *Canad med Ass J*, 70, 317
88 Perinetti, H (1952) *Trans Amer. Ass Goiter*, p. 12
89 Platter, F. (1614) *Observationum in hominis affectibus plerisque*, Basel

The discoveries in respect of inherited deafness and congenital deafness, the sequel of maternal rubella, have clearly revealed the need for making careful inquiries into the family history of persons with deaf-mutism alone in goitrous areas before labelling them the victims of endemic goitre.

REFERENCES

1. Aaron, H H, Schneierson, S J. & Siegel, E. (1955) *J Amer. med. Ass*, 159, 848
2. Ackermann (1790) *Über die Kretinen, eine besondere Menschenabart in den Alpen*, Gotha (Quoted by De Quervain & Wegelin [26])
3. Ainger, L E & Kelly, F C (1955) *J clin. Endocr*, 15, 469
4. Albrecht, W (1934) *Z Hals-, Nasen- u Ohrenheilk*, 36, 262
5. Barker, M H (1946) *Tex St J. Med*, 42, 462
6. Bastenie, P A. (1947) *Lancet*, 1, 789
7. Bell, G O (1952) *Trans. Amer Ass Goiter*, p. 28
8. Benda, C E (1947) *Mongolism and cretinism*, London
9. Blackie, G S. (1855) *Cretins and cretinism*, Edinburgh
10. Bull, G M. & Frazer, R (1950) *Lancet*, 1, 851
11. Cabezas, A, Pineda, T. & Scrimshaw, N S (1953) *Amer. J publ Hlth*, 43, 265
12. Calonne, R (1939) *Ann. Soc. belge Med trop*, 19, 143
13. Campbell, J M H. (1924-25) *Quart J Med*, 18, 191
14. Chen, T. (1952) *J. Formosan med Ass*, 51, 469
15. Clements, F. W (1948) *Med J Aust*, 1, 637
16. Clements, F W. (1953) *Med J. Aust.*, 2, 251
17. Clements, F W (1954) *Med J. Aust*, 2, 894
18. Clements, F. W. (1956) *Metabolism*, 6, 623
19. Costa, A. (1957) *J clin Endocr*, 17, 801
20. Crookshank, F G (1913) *Proc roy Soc. Med (Sect. Dis. Child)*, 7, 26
21. Crotti, A (1935) *Diseases of the thyroid, parathyroids and thymus*, 3rd ed, Philadelphia
22. Davis, L J & Forbes, W. (1945) *Lancet*, 2, 740
23. De Groot, L. J. & Stanbury, J B (1959) *Amer J. Med*, 27, 525
24. Demaeyer, E. M & Vanderborght, H. L. (1953) *Ann. Soc. belge Méd. trop.*, 33, 579
25. De Quervain, F. (1924) *Schweiz Arch Neurol Psychiat*, 14, 3
26. De Quervain, F. & Wegelin, C. (1936) *Der endemische Kretinismus*, Berlin & Wien
27. Dorff, G B (1934) *Amer. J Dis Child*, 48, 1316
28. Eason, J (1939) *Brit. Med J*, 1, 1303
29. Ellerker, A G (1955) *Proc. roy. Soc. Med*, 48, 554
30. Elphinstone, N (1953) *Lancet*, 1, 1281
31. Eugster, J (1938) In *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, Washington, p. 131
32. Fagge, G H (1871) *Med-chir. Trans.*, 54, 155
33. Flaxen, W. (1935) *Acta paediat. (Uppsala)*, 17, 565

[illegible] Turin

[illegible] docr, 7, 47

[illegible] (in press)

39. Gre [illegible]

PHYSIOLOGY OF ENDEMIC GOITRE

JOHN B. STANBURY, M.D.*

Insight into the nature of thyroid disease, as regards both cause and pathologic physiology, has developed through an understanding of the normal function of the thyroid gland. This chapter will be concerned first with a brief account of the physiology of the thyroid and of the metabolic circuit of iodine, and then with a review of the information which is available regarding the functional abnormalities of the human gland when it is deprived of iodine. Comprehensive reviews of thyroid physiology and iodine metabolism are available elsewhere.[3, 31, 32, 52]

The mean daily human consumption of iodine in those parts of the world where endemic goitre does not occur lies above 75 μg. Most of this is in inorganic form. Generally, the organic iodine of the diet is reduced to inorganic iodide prior to absorption, but thyroxine, triiodothyronine, and diiodotyrosine may be absorbed intact. Iodate is rapidly reduced to iodide after intravenous injection.

The iodide concentration of the blood is extremely low, except after ingestion of large amounts. Absorbed iodide has a volume of distribution of 20% to 30% of the body-weight. It does not enter into cells in significant amounts, with the exception of the red blood cells and the cells of the thyroid gland. Soon after absorption, thyroxine (T_4) and 3,3',5-triiodothyronine (T_3) become confined to the vascular compartment of the body as the result of binding to carrier proteins in the plasma. Certain iodinated dyes, such as those used for X-ray visualization of the biliary tree, are also absorbed unchanged and are bound to plasma proteins. A simplified diagram of the metabolic circuit of iodine appears in Fig. 1.

The inorganic iodide of the blood is either excreted by the kidney or taken up by the thyroid. The relative efficiency of these two processes determines the fraction of the iodine of the diet which enters the gland. Application of this principle is the basis of the familiar uptake test of

* Assistant Professor of Medicine, Harvard Medical School, Boston, Mass., USA, Associate Physician, Medical Service, Massachusetts General Hospital, Boston, Mass., USA.

90 Raben, M S (1953) *J. clin. Endocr* , 13, 469
91 Raman, G & Beierwaltes, W. H. (1959) *J clin. Endocr.*, 19, 228
92. Richards, C. E., Brockhurst, R J. & Coleman, T. H (1949) *J. clin. Endocr* , 9, 446
93 Rienhoff, W F , jr (1931) *Medicine (Baltimore)*, 10, 257
94. Rundle, F F. (1951) *Joll's diseases of the thyroid gland*, London
95. Salm, R (1954) *J Obstet. Gynaec. Brit Emp.*, 61, 831
96. Sardinia, Commissione nominata d'ordine di S M. il re di Sardegna per studiare il cretinismo (1848) *Relazione della comissione* . . , Torino
97 Saxèn, E A & Saxèn, L. O (1954) *Docum Med. geogr trop. (Amst.)*, 6, 335
98. Scrimshaw, N S (1954) *Bol Ofic. sanit panamer* , 36, 277
99 Shore, R A & Andrew, R. L (1929) *Goitre in school-children*, Wellington, N Z.
100 Silberschmidt, W (1928) *Die Prophylaxe des endemischen Kropfes* In. *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 498
101 Smallpiece, V (1949) *Lancet*, 1, 565
102 Smeby, B (1953) *Nord Med* , 50, 1304
103 Sokal, J E (1954) *J Amer med Ass* , 154, 1321
104. Spence, A W. (1952) *Brit. med J.*, 2, 529
105. Spencer, J G. C (1954) *Brit J Cancer*, 8, 393
106 Spencer, J G. C (1955) *Proc roy Soc Med* , 48, 554
107 Stacpoole, H H (1953) *Bull Wld Hlth Org* , 9, 283
108 Stanbury, J B. & Hedge, A N (1950) *J clin Endocr* , 10, 1471
109 Stanbury, J B. & Querido, A (1957) *J clin Endocr.*, 17, 803
110 Stocks, P. (1927) *Biometrika*, 19, 292
111. Stott, H. et al (1931) *Indian J med Res* , 18, 1059
112 Stott, H & Gupta, S P (1934) *Indian J. med Res* , 21, 655
113 Swan, C. et al (1943) *Med J Aust* , 2, 201
114. Tait, L. (1875) *Edinb. med J* , 20, 993
115 Várbiro, B , Száva, I & Koch, S. (1953) *Gyermekgyógyászat*, 4, 10
116 Warkany, J & Selkirk, T K. (1955) *Amer J Dis Child*, 89, 144
117. Wegelin, C. (1926) *Münch. med. Wschr* , 71, 1554
118 Wegelin, C (1946) *Praxis*, 35, 601
119 Wilkins, L , Clayton, G. W & Berthrong, M. (1954) *Pediatrics*, 13, 235
120. World Health Organization, Study-Group on Endemic Goitre (1953) *Bull. Wld Hlth Org.*, 9, 293
121 Wyndham, N. (1940) *Med. J Aust* , 1, 756

Trapping depends upon cellular integrity and respiration,[41, 51] and upon the presence of sulfhydryl groups[13] Oxidative phosphorylation is also involved in the trapping of iodide.[13]

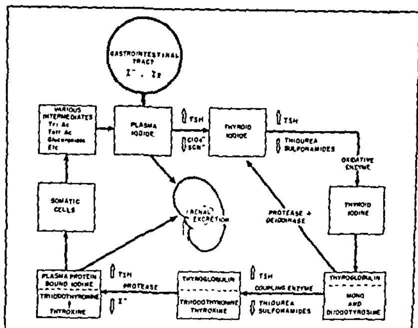
Thiocyanate and perchlorate ions prevent iodide trapping,[49, 53] perchlorate being about ten times as potent as thiocyanate. If either of these substances is administered after trapping has occurred, trapped iodide is rapidly released from the gland, but iodine which has been chemically bound to iodinated tyrosines or thyronines is retained Chronic administration of thiocyanate may cause goitre, a result that has been observed in certain patients treated with this substance for hypertension It is not known whether thiocyanate and perchlorate ions block trapping by interfering with cell-membrane transport, or by competing for binding sites within the gland

The trapped iodide of the gland is oxidized by an oxidative system of the thyroid cell and immediately attaches itself at the 3-position or at the 3- and 5-positions of the benzene ring of tyrosyl residues, which are present in peptide linkages. This step is specifically blocked by the antithyroid drugs related to thiourea Fawcett and Kirkwood[12] have described a tyrosine-oxidase system which they believe to be responsible for the formation of monoiodotyrosine. Monoiodotyrosine appears in homogenates of thyroid tissue incubated with added ^{131}I [8, 18, 41] Under normal circumstances, neither monoiodotyrosine nor diiodotyrosine escapes into the circulation [45] The oxidation of iodide and iodination of the tyrosyl residues may simply proceed side by side, or the iodide may first be activated to an intermediate storage form of iodine which requires the presence of a transferring enzyme before it can react with the tyrosine. Free or peptide-linked tyrosine is iodinated by iodine without the agency of enzymes *in vitro*, but it is probable that, in the gland, the rate at which iodination proceeds is governed enzymatically

There is evidence that peroxidase is concerned in iodide oxidation Not only has peroxidase activity been demonstrated many times in thyroid tissue, but the oxidation of iodide, which is rather specific to thyroid tissue, is inhibited by catalase. Further, a variety of substances, such as thiourea and resorcinol, which inhibit the conversion of iodide to organic compounds by thyroid slices or *in vivo*, either inhibit the peroxide-peroxidase system or act as competitive substrates for it [38]

It has been suggested that the only requirements for iodide oxidation are oxidizing conditions and the presence of large amounts of iodide; this implies that there may be no specific iodide oxidizing system in the thyroid gland The colloid has a high oxidation-reduction potential, but this is lowered by substances which have antithyroid activity, such as thiouracil[10] The possibility remains that a specific electron-transfer system exists for converting iodide to iodine.

FIG 1. SIMPLIFIED DIAGRAM OF METABOLIC CIRCUIT OF IODINE



The solid arrows represent the direction of flow. The open arrows indicate stimulation, if pointing upwards, and inhibition, if pointing downwards

thyroid function using radioactive iodine. The normal kidney clears of its contained iodide approximately 35 ml. of plasma per minute. The normal clearance of iodide by the thyroid is slightly less, but may be much more if the patient has been deprived of iodine. Renal clearance of the iodide is not altered by iodine deficiency in man

Accumulation of Iodide by the Thyroid

The resting thyroid maintains a concentration of iodide against the plasma which is normally of the order of twenty to one but may increase to several hundred to one in the hyperplastic gland. The thyroid/plasma ratio is governed by the thyrotropic hormone, but it is also influenced by the quantity of stored iodine within the gland itself.[18, 50] The ratio is constant over a wide range of plasma concentration of iodide, but with increasing concentration the ratio eventually falls toward 0 5 : 1 as the trapping capacity of the gland approaches saturation.

Trapped iodine is exchangeable with the iodide of the blood; it is found not only in the parenchymal cells, but in the colloid as well[25, 53]

normal thyroid tissue.[27] It is interesting and possibly relevant to the problem of endemic goitre that diiodotyrosine has been tentatively identified in the serum of two patients with "endemic cretinism" in northern Italy.[6]

One of the principal unsolved problems of the thyroid is the nature of thyroglobulin with respect to the iodinated amino-acids There is every reason to suspect that thyroglobulin may contain widely varying amounts of these amino-acids, and yet such variability in amino-acid content and in the sequence of amino-acids is not in keeping with current concepts of the specificity of protein structure. It may be that the amino-acid sequence is fixed but that the degree of iodination can vary, or that the iodinated amino-acids are at N-terminal or C-terminal positions and can vary without altering the backbone of the thyroglobulin molecule. Roche et al.[34] have found that in pork thyroglobulin some of the T_4, DIT, and tyrosine residues occupy N-terminal positions. Most of the DIT and T_4 residues were internal. T_3 and MIT were not found at N-terminal positions. Pancreatin released MIT first, followed by DIT, from thyroglobulin T_3 and T_4 came off more slowly.[48] Little else is known of the fine structure of thyroglobulin

It is possible that the strongly stimulated thyroid gland may secrete newly formed thyroid hormones directly into the blood,[42] but under normal circumstances T_3 and T_4 are released as needed from the thyroglobulin. The proteases and peptidases which have been extracted from the thyroid lack specificity for thyroglobulin The protease has a pH optimum of 3 5 and is much more effective against haemoglobin than against thyroglobulin The peptidase has a pH optimum near the neutral point

Circulating Hormone

Thyroxine comprises 60% to 90% of the circulating iodine. The remainder is triiodothyronine and possibly 3,3'-diiodothyronine Circulating thyroxine is tightly bound to a specific carrier protein which has an electrophoretic mobility very close to that of α_2-globulin A small fraction of thyroxine is also bound to albumin Triiodothyronine is more loosely bound to protein and is more generally distributed among the various serum components Thyroxine and triiodothyronine can be removed from the blood by extraction with acid butanol Significant variations in ratios among the iodinated components of the serum have not been definitely associated with specific disease states

The quantity of circulating iodine in the serum which is precipitable with the serum proteins (PBI; SPI) serves as a useful measure of thyroid function Normal values lay between 3.5 and 8 μg per 100 ml Concentrations below 3 5 suggest hypothyroidism, unless prior administration of certain iodinated substances, such as those used in visualization of the gall

Hormone Formation

The generally accepted pathway of hormone formation is by condensation of two iodotyrosine residues, with extrusion of an alanine group. Conceivably, a variety of substances could be formed, and the number is still greater if one of the condensing residues is tyrosine itself. The possibilities are as follows:

3,5-diiodothyronine
3',5'- "
3,3'- "
3-monoiodothyronine
3'- "
3,5,3'-triiodothyronine
3,3',5' "
3,3',5,5'-tetraiodothyronine (thyroxine)

Thyroxine was the first of these compounds to be identified in the gland. The discovery by Gross & Pitt-Rivers [15] in 1952 that 3,3',5-triiodothyronine is present in the thyroid has been followed by the important studies of Roche and his colleagues [35] which have indicated that several other iodinated thyronines may also be found in the gland. Prominent among these is 3,3'-diiodothyronine. It has not yet been shown with certainty that the scheme of formation of the iodinated substances of the gland is indeed that described above, nor is it certain that any substance other than thyroxine is secreted by the gland

Storage and Release

The iodinated tyrosines and thyronines of the gland are stored in peptide linkages as components of the thyroglobulin Normally, and under conditions of increased glandular activity, the thyroid cells may secrete hormone directly into the blood without intermediary storage. Thyroglobulin is a compound of high molecular weight which is broken down by the action of cathepsins [9, 23] into components which are small enough to traverse the epithelial cells of the gland and enter the body The fate of the monoiodotyrosine (MIT) and diiodotyrosine (DIT) released in the course of proteolysis of thyroglobulin was unknown until Roche et al [33] postulated and found a specific deiodinase in the gland which removes iodine from these two compounds. Thus, normally, they do not reach the peripheral blood. Several patients with congenital goitre and hypothyroidism have been described who appear to lack the tissue deiodinase.[43] Large amounts of monoiodotyrosine and diiodotyrosine were found in the peripheral blood of these patients, and tissue slices from the thyroid gland of one of them were unable to dehalogenate diiodotyrosine, in contrast to

normal thyroid tissue.[27] It is interesting and possibly relevant to the problem of endemic goitre that diiodotyrosine has been tentatively identified in the serum of two patients with "endemic cretinism" in northern Italy.[6]

One of the principal unsolved problems of the thyroid is the nature of thyroglobulin with respect to the iodinated amino-acids There is every reason to suspect that thyroglobulin may contain widely varying amounts of these amino-acids, and yet such variability in amino-acid content and in the sequence of amino-acids is not in keeping with current concepts of the specificity of protein structure. It may be that the amino-acid sequence is fixed but that the degree of iodination can vary, or that the iodinated amino-acids are at N-terminal or C-terminal positions and can vary without altering the backbone of the thyroglobulin molecule. Roche et al [31] have found that in pork thyroglobulin some of the T_4, DIT, and tyrosine residues occupy N-terminal positions. Most of the DIT and T_4 residues were internal T_3 and MIT were not found at N-terminal positions. Pancreatin released MIT first, followed by DIT, from thyroglobulin. T_3 and T_4 came off more slowly.[43] Little else is known of the fine structure of thyroglobulin.

It is possible that the strongly stimulated thyroid gland may secrete newly formed thyroid hormones directly into the blood,[42] but under normal circumstances T_3 and T_4 are released as needed from the thyroglobulin The proteases and peptidases which have been extracted from the thyroid lack specificity for thyroglobulin The protease has a pH optimum of 3 5 and is much more effective against haemoglobin than against thyroglobulin. The peptidase has a pH optimum near the neutral point

Circulating Hormone

Thyroxine comprises 60% to 90% of the circulating iodine The remainder is triiodothyronine and possibly 3,3'-diiodothyronine Circulating thyroxine is tightly bound to a specific carrier protein which has an electrophoretic mobility very close to that of α_2-globulin A small fraction of thyroxine is also bound to albumin Triiodothyronine is more loosely bound to protein and is more generally distributed among the various serum components Thyroxine and triiodothyronine can be removed from the blood by extraction with acid butanol Significant variations in ratios among the iodinated components of the serum have not been definitely associated with specific disease states.

The quantity of circulating iodine in the serum which is precipitable with the serum proteins (PBI, SPI) serves as a useful measure of thyroid function Normal values lay between 3.5 and 8 μg per 100 ml Concentrations below 3 5 suggest hypothyroidism, unless prior administration of certain iodinated substances, such as those used in visualization of the gall

bladder, has obscured the test. The rate at which the circulating hormones are used (and replenished in the equilibrium state) depends at least in part upon their concentration Normally, the thyroid gland secretes between 100 and 200 μg of hormonal iodine daily, and this is turned over in the periphery at a rate of approximately 10% per day. The secretion rate and the turnover are faster in patients with hyperthyroidism.

Perhaps the most subtle and difficult problem in the study of the thyroid has been the nature of the reaction produced upon cells by the thyroid hormone It has been suggested that the hormone dissociates (uncouples) oxidative phosphorylation, so that oxidation proceeds without the formation of a proportional amount of phosphate bond energy.[17, 35, 42] There is perhaps less evidence to support other theories which have been proposed.

Much of the iodine from the thyroid hormones is split off and returned to the plasma as iodide to re-enter the metabolic cycle. Some of the hormone may be conjugated or partially degraded, and appear in this altered form in the bile and possibly also in the urine

Control of Function

The thyroid gland is under tripartite control. The best understood of these regulatory mechanisms is the anterior-pituitary—thyroid relationship. The rate of secretion of thyroid-stimulating hormone (TSH) depends upon the concentration of thyroid hormones circulating in the blood Secretion of TSH can be inhibited by administration of appropriate amounts of thyroxine or of triiodothyronine. When the thyroid is removed, the production of TSH increases, at least for a time Removal of the hypophysis results in a reduction of thyroid function, and in man thyroid activity may be suppressed completely.[24] Thus, the TSH-producing cells of the hypophysis and the thyroid appear to exist in a dynamic state of balance (feed-back)

The circulating thyroid hormones in the plasma may have a direct regulatory effect upon thyroid function. Cortell and Rawson[5] observed that the size and cell height of the thyroid gland of TSH-treated hypophysectomized rats could be influenced by various doses of thyroxine. Their observations are subject to the alternative explanation that the exogenous thyroxine may have altered the rate of disposal of the exogenous TSH. Halmi[16] has found that the responses of the gland are dependent in part upon the iodine content of the gland Supporting evidence has been furnished by VanderLaan & Caplan[50] and by Wahlberg.[51]

It can be seen that the regulation of the gland is complex and incompletely understood The relative contribution of the several regulatory influences is not known, nor is it known to what degree the various metabolic steps in the gland can be separately and independently influenced TSH stimulates all aspects of glandular activity, such as iodine uptake, phos-

phorus uptake,[20] hormone release, etc , but equal stimulation does not always occur because there are states of disequilibrium where the gland is storing iodine faster than it is secreting hormonal iodine, or *vice versa*.

Iodine Deficiency and Endemic Goitre

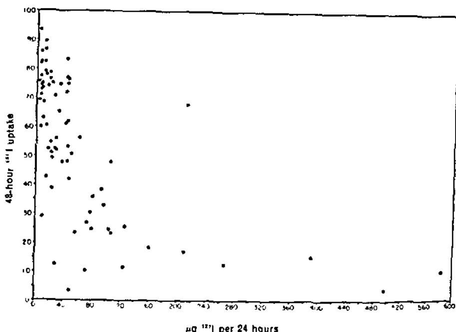
There is a vast amount of information on the effect of iodine deficiency on the function of the rat thyroid Hyperplasia of the gland can be readily produced,[30] and this effect can be enhanced by feeding chloride,[1] but chloride has no similar noteworthy iodouretic effect in man (D. S. Riggs & J. B Stanbury, unpublished data) Calcium also causes enhanced growth of the iodine-deprived rat thyroid [46] Querido et al.[26] have found that in rats deprived of iodine there is a relative increase in the amount of labelled iodine which is present in the monoiodotyrosine fraction of the gland It is beyond the scope of this chapter to review all the findings from animal studies The reader is referred to the paper of Barker [2] for an introduction to the literature concerning the general physiology of the thyroid. This chapter will be principally concerned with studies which have been made upon patients and where the weight of evidence has indicated iodine deprivation as the sole predisposing factor. With few exceptions, study of endemic goitre as performed with modern methods has consistently furnished information which has been in accord with a situation of iodine deficiency in the diet

If the assumption is made that patients are nearly in equilibrium with their environment in respect to dietary iodine, then the daily urinary excretion of iodine can serve as a most useful index of the quantity of iodine which the patient is ingesting Surveys of the urinary excretion of iodine by subjects living in endemic goitre regions have disclosed a mean iodine excretion which is much lower than that of persons in areas where endemic goitre does not exist (the Netherlands,[29] Argentina,[42] Venezuela,[37] Finland [21]) Daily excretion rates of less than 10 μg may be a commonplace.

In the limited number of observations which have been made, the serum-precipitable iodine of patients with endemic goitre has not been far different from that of normal control subjects Lamberg, Wahlberg, and Kuhlback[19] found that certain of their patients with goitre in Finland had subnormal values for SPI Observations in endemic goitre areas made by Terpstra [47] using ^{127}I showed normal PBI values, both in patients with goitre (5.2$\pm$SD 0 5), and in control subjects (5 6$\pm$SD 1 0) The statistical dispersion of serum concentrations found among patients in western Argentina was greater than in a control series, but the mean value was very nearly the same [42]

The low ingestion of iodine is reflected in the increased avidity of the thyroid gland for iodine This is illustrated in Fig 2, which is taken from a study of endemic goitre in western Argentina [42] It is seen from the figure that, with considerable uniformity, patients with low amounts of iodine in

FIG. 2. RELATIONSHIP BETWEEN EXCRETION OF IODINE AND UPTAKE OF RADIOACTIVE IODINE IN A GROUP OF PATIENTS FROM WESTERN ARGENTINA

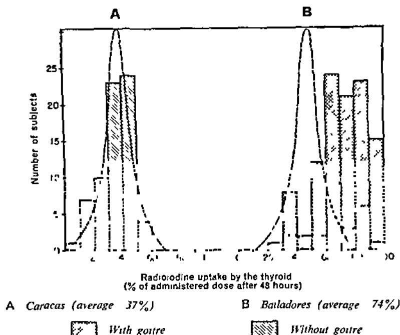


Reproduced by kind permission of the editors of the Journal of Clinical Endocrinology and Metabolism

the urine demonstrated a high avidity for iodine, as indicated by the enhanced uptake of ^{131}I, whereas those patients who had succeeded in obtaining an adequate supply of iodine exhibited uptake values which would be considered normal in non-endemic regions. Entirely similar findings have been obtained in the Netherlands [47] and in Finland [21]

The uptake of iodine by the thyroid of the patient with endemic goitre is usually found to be greater than normal. This was recognized long ago from a study carried out with the stable isotope of iodine [11] and has been amply confirmed by more direct measurements made recently [21, 37, 42, 47] with ^{131}I A typical study illustrating this fact is shown in Fig 3. The authors [37] have compared their findings in an endemic area (Bailadores) and a non-endemic area (Caracas) of Venezuela with those obtained by Skanse [40] in a group of normal subjects observed in Boston, Massachusetts While there is an overlap between the two curves of distribution, many patients with endemic goitre have uptake values which would be higher than normal if found in patients from a non-endemic district In an isolated mountainous area of Venezuela, Roche [36] has observed high uptake values of ^{131}I in subjects without goitre. Obviously, the ^{131}I uptake test has serious limitations and may be of no value in patients from a non-endemic district This has proved

FIG. 3. COMPARISON OF RADIOIODINE UPTAKE BY PATIENTS IN A NON-ENDEMIC ZONE (CARACAS) AND AN ENDEMIC ZONE (BAILADORES) OF VENEZUELA



Reproduced from Roche et al[29] by kind permission of the editors of the *Journal of Clinical Endocrinology and Metabolism*

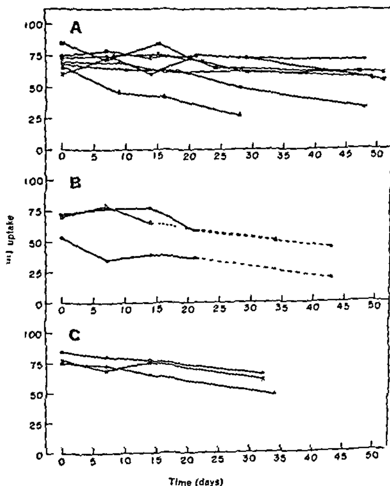
to be an awkward problem in applying the uptake test to clinical situations in endemic regions

The pioneer work of Greer and his associates [14] on the effect of certain foods on thyroid function has indicated the possibility that in certain cases endemic goitre might be the result of a specific goitrogen in the diet Such substances inhibit the uptake of iodine by the gland. In Tasmania, Clements[4] has found that milk from dairy cows fed upon chou-moellier (marrow-stem kale), a plant of the *Brassica* genus, may, upon ingestion, inhibit the accumulation of radioactive iodine in the thyroid gland. On the other hand, A. Costa (personal communication) has found the uptake to be the same in the inhabitants of certain goitrous areas of Italy as in normal control subjects He has also found high uptake values for ^{131}I in subjects with endemic cretinism, together with normal to high readings for the protein-bound iodine content of the serum [7] On the other hand, Raman & Beierwaltes[28] have found the PBI values to be somewhat lower in cretinous than in normal subjects

If iodine is restored to the daily diet of the iodine-deprived subject, there is a slow readjustment of iodine retention until a new state of balance is

achieved, and during this period there is a net gain of iodine in the thyroid gland. The net gain depends upon the initial degree of depletion and the size of the daily supplement. The adjustment to a new equilibrium state may take several weeks or longer. These principles are illustrated in Fig. 4. Groups of patients with endemic goitre and limited dietary iodine were left on their own household diets and were given supplements of potassium iodide in various amounts. The period of observation was not long enough

FIG. 4. EFFECT OF DAILY SUPPLEMENTARY DOSES OF POTASSIUM IODIDE ON UPTAKE OF RADIOIODINE BY PATIENTS FROM AN ENDEMIC AREA OF ARGENTINA



A. *Patients given 150 μg of KI daily*

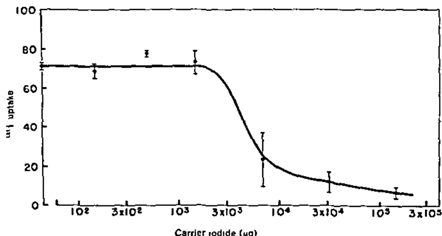
B. *Patients given 500 μg (solid line) and 600 μg (broken line) of KI daily*

C *Patients given 1500 μg of KI daily*

for complete readjustment to take place, but the trend was evident. When the daily supplement was 150 μg, the net retention of iodine was estimated to be 5 8 mg in 99 days. When the supplement was 1500 μg daily, the retention was 34.1 mg over a period of 33 days. One of the patients in the latter group subsequently developed thyrotoxicosis.

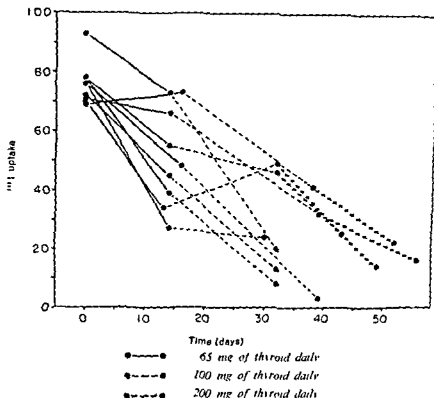
The fraction of a single dose of iodine retained by a patient with endemic goitre is constant over a wide range, but at higher dose levels the fraction decreases as the capacity of the gland to absorb iodine from the blood approaches saturation. A group of patients with endemic goitre were given control tracer doses of ^{131}I, and later tracers of ^{131}I supplemented with widely varying amounts of carrier ^{127}I The results (Fig 5) suggest that most of the iodine above 5 mg is rapidly excreted by the kidney.

FIG 5. EFFECT OF A SINGLE DOSE OF IODINE ON THYROIDAL UPTAKE OF SIMULTANEOUSLY ADMINISTERED RADIOIODINE



Both in normal subjects and in those with endemic goitre, administration of desiccated thyroid inhibits the activity of the gland, presumably by causing diminished production of TSH by the anterior pituitary Observations on a group of subjects with endemic goitre are illustrated in Fig 6 In 7 out of 9 patients, 65 mg daily of desiccated thyroid caused a significant fall in uptake of radioiodine Increasing the daily dose to 100 mg caused a further fall in uptake in all but one patient These responses are comparable to those observed in normal patients, and much greater than those seen after administration of thyroxine or triiodothyronine to patients with Graves' disease, where initial uptake values are comparable to those seen in endemic goitre patients These observations are consistent with the interpretation that the thyroid gland of the patient with endemic goitre is under an increased stimulus from

FIG 6. EFFECT OF ORALLY ADMINISTERED DESICCATED THYROID ON UPTAKE OF RADIOIODINE IN PATIENTS WITH ENDEMIC GOITRE IN WESTERN ARGENTINA

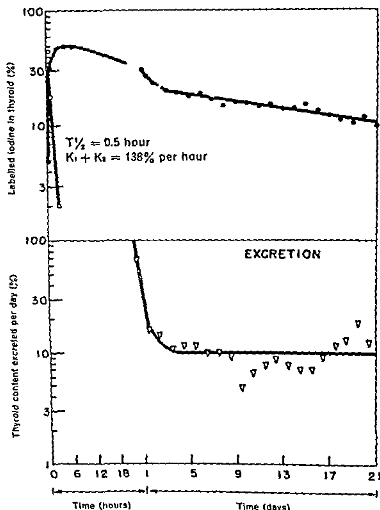


the anterior pituitary gland, or that the thyroid is more susceptible to TSH stimulation.

The iodine content of the endemic goitrous gland varies widely, but the *concentration* of iodine in the gland is usually lower than normal. These observations were made long ago by direct analysis of glands surgically removed.[39] The thyroid iodine content has also been calculated from urinary measurements of ^{127}I and ^{131}I after a tracer dose of ^{131}I, and from *in vivo* data obtained from patients with endemic goitre.[43] These values varied from 260 to 12 600 μg of iodine in seven patients studied. It was observed that the release of labelled iodine from the gland depended upon the quantity of iodine contained therein. Those patients whose thyroid iodine was high appeared to discharge labelled iodine from the gland at a net rate which was proportional to the contained iodine. No such simple relationship was obtained when the thyroidal iodine was low; in this case, the patients released labelled iodine in such a way as to suggest that it was being given up by two separate and distinct compartments in the gland. One of these was thought to be the cells, which were releasing newly formed

hormone rapidly and directly into the blood. This compartment was small and had a rapid turnover. The other was thought to be a larger compartment with a much slower turnover, possibly the colloid stores The type of release shown by a patient with low thyroid iodine content is illustrated in Fig. 7. Similar curves may be seen in patients with vigorous thyrotoxicosis. In

FIG. 7. RELEASE OF LABELLED IODINE AND ITS APPEARANCE IN THE URINE OF A PATIENT WITH ENDEMIC GOITRE AND LOW THYROIDAL CONTENT



Note the rapid initial release during the first five days after administration.
T½ = half-time of iodine disappearance
K_1 = thyroidal uptake constant
K_2 = renal excretion constant

patients with endemic goitre Terpstra [47] found that the average PBI values 24 hours after administration of a tracer dose of ^{131}I were within normal limits (<0.35% of the dose per litre of serum; see table below). These observations led to the conclusion that the total thyroid iodine content in the investigated cases did not differ from the total iodine content of normal glands.

URINE IODINE EXCRETION AND PBI VALUES OF A GROUP OF PATIENTS WITH ENDEMIC GOITRE IN THE NETHERLANDS

Sex	Age	Thyroid size (times normal)	Total urine ^{127}I excretion per 24 hours * (µg)	$PB^{127}I$ (µg %)	$PB^{131}I$ after 48 hours (% dose per litre)	Conversion ratio ** after 24 hours (%)
F	31	4-5	43	5.0	0.07	72
F	23	2-3	33	6.0	0.06	64
F	31	3	24	6.0	0.09	79
F	32	4-5	42	4.9	0.078	59
F	21	5	27	5.1	0.026	82
F	18	5	52	4.5	0.025	50
F	16	4-5	32	5.3	0.045	42
F	26	2	14	5.6	0.11	87
F	25	3	17	6.8	0.044	81
M	37	3-4	17	5.8	0.04	65
F	16	6	15	5.3	0.047	50

* Average figures of 2-5 observations

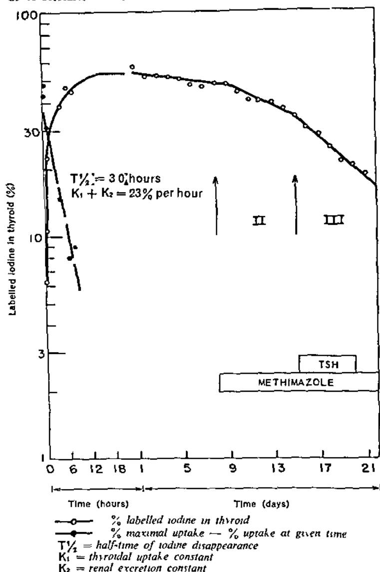
** Conversion ratio = $\frac{\text{serum } PB^{131}I}{\text{total serum } ^{131}I}$

After Terpstra [47]

The thyroid gland of the endemic goitre patient is responsive to certain antithyroid drugs and to thyrotropic hormone Administration, for example, of methimazole (1-methyl-2-mercapto-imidazole), causes an accelerated release of labelled iodine from the gland as the drug produces its characteristic inhibition of re-utilization of iodine released through the peripheral degradation of hormone (Fig 8). Further increase in the rate of release of iodine from the gland occurs when thyrotropin is administered. The latter observation indicates that these glands are responsive to exogenous thyrotropin even though they are already being stimulated by that hormone.

There are fragmentary data which suggest that there may be qualitative abnormalities of iodine metabolism in endemic goitre. G. Escobar & F. Escobar del Rey (personal communication), studying endemic goitre near Granada, Spain, have found that certain patients, although not all, may have a considerable fraction of serum iodine which is precipitable

FIG. 8. EFFECT OF AN ANTI-THYROID DRUG, METHIMAZOLE, AND A THYROTROPIC HORMONE ON THE RELEASE OF LABELLED IODINE FROM THE THYROID OF A PATIENT WITH ENDEMIC GOITRE IN WESTERN ARGENTINA



with the usual protein precipitants and is extractable into acid butanol, but which, unlike thyroxine and triiodothyronine, is extractable from butanol by alkali The nature of this substance is not known. The observation of Costa et al.[8] that two out of ten subjects with endemic cretinism had diiodo-

tyrosine in the blood may be important and needs confirmation and further study. Apart from this, there is no evidence that an abnormal iodinated component is present in the blood of patients with endemic goitre.

REFERENCES

1. Axelrad, A A, Leblond, C. P. & Isler, H. (1955) *Endocrinology*, 56, 387
2. Barker, S. B (1955) *Ann. Rev Physiol*, 17, 417
3. Berson, S. A (1956) *Amer J. Med*, 20, 653
4. Clements, F. W. (1955) *Med J Aust*, 2, 369
5. Cortell, R & Rawson, R W (1944) *Endocrinology*, 35, 488
6. Costa, A, Cottino, F., Ferraris, G M, Marchis, E, Marocco, F., Mortara, M. & Pietra, R (1953) *Medicina (Parma)*, 3, 455
7. Costa, A, Mortara, M., Cottino, F., Pellerito, N. & Dell'Acqua, R. (1959) *Ann. Endocr*, 20, 237
8. De Groot, L J & Carvalho, E. (1960) *J. Biol. Chem*, 235, 7
9. De Robertis, E (1949) *Ann. N Y Acad Sci*, 50, 317
10. De Robertis, E & Garro, R (1946) *Endocrinology*, 38, 137
11. Elmer, A. W (1938) *Iodine metabolism and thyroid function*, London, Oxford University Press
12. Fawcett, D M & Kirkwood, S. (1954) *J biol. Chem*, 209, 249
13. Freinkel, N. & Ingbar, S. H (1955) *J clin Endocr.*, 15, 598
14. Greer, M. A (1950) *Physiol Rev*, 30, 513
15. Gross, J. & Pitt-Rivers, R (1952) *Lancet*, 1, 593
16. Halmi, N. S (1954) *Endocrinology*, 54, 216
17. Hoch, F. L & Lipmann, F. (1954) *Proc. nat. Acad Sci. (Wash)*, 40, 909
18. Lamberg, B.-A, Matovinovic, J. & Stanbury, J. B. (1958) *Acta endocr. (Kbh)*, 29, 33
19. Lamberg, B.-A, Wahlberg, P & Kuhlback, B (1956) *Nord Med*, 55, 354
20. Lamberg, B -A, Wahlberg, P. & Olin-Lamberg, C (1955) *Acta endocr (Kbh)*, 19, 263
21. Lamberg, B -A, Wahlberg, P., Wegelius, O, Hellström, G & Forsius, P. I (1958) *J clin Endocr*, 18, 991
22. Lardy, H A & Maley, G F. (1954) *Recent Progr. Hormone Res*, 10, 129
23. Laver, W. G & Trikojus, V. M (1955) *Biochim biophys Acta*, 16, 592
24. Li, M C., Rall, J. E, MacLean, J P, Lipsett, M B, Ray, B S & Pearson, O H (1955) *J. clin Endocr*, 15, 1228
25. Pitt-Rivers, R. & Trotter, W R. (1953) *Lancet*, 2, 918
26. Querido, A., Schut, K. & Terpstra, J. (1957) *Hormone synthesis in the iodine-deficient thyroid gland.* In: Wolstenholme, G. E & Millar, E. C P., ed, *Regulation and mode of action of thyroid hormones* (*Ciba Foundation colloquia in endocrinology*, vol 10), London, Churchill, p 124
27. Querido, A., Stanbury, J. B., Kassenaar, A A H & Meijer, J. W. A. (1956) *J. clin Endocr.*, 16, 1096
28. Raman, G & Beierwaltes, W. H. (1959) *J clin Endocr*, 19, 228
29. Reith, J F. (1933) *Schweiz med. Wschr.*, 63, 791
30. Remington, R E. (1932) *J. biol Chem*, 97, CI

[illegible] 4, 270

[illegible] y, 35, 583

[illegible] y, S (1952) *Biochim biophys Acta*, 9, 161

[illegible] be, G (1955) *C. R. Acad. Sci (Paris)*, 240, 404

35. Roche, J, Michel, R, Wolf, W. & Nunez, J. (1956) *Biochim biophys Acta*, **19**, 308
36 Roche, M. (1959) *J clin Endocr.*, **19**, 1440
37. Roche, M, De Venanzi, F, Vera, J, Coll, E, Spinetti-Berti, M, Mendez-Martini, J., Gerardi, A. & Forero, J (1957) *J. clin Endocr*, **17**, 99
38. Rosenburg, I N (1952) Science, **116**, 503
39. Salter, W. T. (1940) *The endocrine function of iodine*, Cambridge, Mass, Harvard University Press
40 Skanse, B (1949) *Acta med scand*, Suppl. No 235
41. Slingerland, D W. (1955) *J clin Endocr*, **15**, 131
42. Stanbury, J B, Brownell, G L, Riggs, D S, Perinetti, H, Itoiz, J. & Castillo, E. B del (1954) *Endemic goiter The adaptation of man to iodine deficiency*. Cambridge, Mass, Harvard University Press
43. Stanbury, J B, Meijer, J W A & Kassenaar, A A H (1956) *J. clin. Endocr*, **16**, 848
44 Taurog, A, Potter, G. D & Chaikoff, I L (1955) *J biol Chem*, **213**, 119
45. Taurog, A, Wheat, J D & Chaikoff, I L (1956) *Endocrinology*, **58**, 121
46 Taylor, S (1954) *J. clin Endocr*, **14**, 1412
47. Terpstra, J (1956) *De schildklierfunctie bij endemische krop*, Leiden (Thesis)
48 Tong, W. & Chaikoff, I L (1958) *J biol Chem*, **232**, 939
49 VanderLaan, W P. & Bissell, A (1946) *Endocrinology*, **39**, 157
50 VanderLaan, W. P & Caplan, R (1954) *Endocrinology*, **54**, 437
51. Wahlberg, P (1955) *Acta endocr (Kbh)*, Suppl. No 23
52 Wolff, J & Goldberg, R C (1957) *Disorders of iodine metabolism* In Thompson, R H S & King, E J ed, *Biochemical disorders in human disease*, New York, Academic Press, p 389
53 Wollman, S H & Wodinsky, I (1955) *Endocrinology*, **56**, 9
54 Wyngaarden, J B, Stanbury, J B & DuToit, C H (1951) *J clin Endocr*, **11**, 1259
55 Wyngaarden, J B, Wright, B M & Ways, P (1952) *Endocrinology*, **50**, 537

THE STUDY OF EXPERIMENTAL GOITRE

Professor STEPHAN MILCU *

Introduction

Research on experimental goitre offers an opportunity of studying the factors involved in the appearance of goitre and their mode of action, as well as changes in the structure and function of the thyroid and their effects on the body. It is thus possible to conduct experiments based on the conditions obtaining in endemic areas and to study the various factors encountered there

At the beginning of our research we took it for granted that endemic goitre required for its explanation a shortage of iodine acting concurrently with a secondary hypersecretion of pituitary thyrotropic hormone (thyroid-stimulating hormone TSH) and with other factors influencing pituitary thyrotropic action and thyroid function Our present knowledge of iodine metabolism raises the question whether there exists an iodine shortage of endogenous origin, due to various causes—faulty intestinal absorption, faulty uptake by the thyroid, or excessive excretion of iodine. In endemic areas these various factors clearly come into the picture by aggravating iodine shortage of exogenous origin; in non-endemic areas they are responsible for the appearance of sporadic goitre

The recent work of Cassano et al [5] shows in what clinical conditions goitre may appear We, too, have studied the possible effects of certain hormones on the thyroid in which a kind of endogenous iodine shortage appears as a secondary manifestation The existence of these hormonal forms of goitre receives clinical confirmation in the goitre of puberty and of pregnancy

Although knowledge of the role of the nervous system in the production of goitre is limited, some mention should be made of the part known to be played by the diencephalon in increasing the output of TSH when the diet is deficient in iodine and of the action of the autonomic system on the thyroid We have also carried out research in this field

* Member of the Academy and Director of the Academy Institute of Endocrinology, Bucarest, Romania

The lesions of endemic goitre are very polymorphic, and develop slowly and continuously. First to appear are the lesions found in parenchymatous colloid goitre; then the lesions of nodular goitre develop, and finally those of degenerative fibrous conditions of the thyroid. While the first stages of this process are explicable in terms of stimulation by TSH caused by lack of iodine, the occurrence of the subsequent stages is less easy to understand. It may be assumed that thyroid antibodies are involved, and are able to aggravate the initial goitrogenic lesions

From the beginning of our research we have accepted the iodine deficiency theory—the theory that iodine deficiency is an essential factor in the production of goitre, whatever the exact process culminating in the goitre We have hardly touched on the agents responsible for iodine deficiency, studying rather the endogenous factors involved in an increased or decreased response of the thyroid to an inadequate supply of iodine From this standpoint we have taken a very wide view of the problem, being ready to regard any factor at all as capable of affecting iodine metabolism and especially of preventing iodine from being taken up by the gland or taking part in hormone synthesis Our research work has been spread over nearly ten years and carried out in the face of many vicissitudes—hence its incompleteness

Our results make a small contribution to knowledge of experimental goitre Goitre has been produced experimentally by a diet rich in cabbage,[6] by a diet poor in iodine,[15] by sulfaguanidine,[17] and by thiouracil.[3] We have used these different experimental methods to produce goitres in rabbits, guinea-pigs, and rats; but we also studied the effects of variations of neural or hormonal function and of auto- or iso-immunization. The results in some cases were unexpected and difficult to interpret—for instance, with the long-term changes in the level of iodine in the blood, in oxygen consumption, and in iodine uptake after injection of Novocaine or rubber into the thyroid These results throw some light on the unfavourable effects of sclerotic lesions in the thyroid, which behave, in fact, as inclusion bodies. Our most recent studies are on the relationships between the pathology of thyroid immunization and the development of deficiency or drug-induced goitre. As in the other experimental fields, our results raise more problems than they solve.

Influence of the Central Nervous System on Experimental Goitre

The influence of the nervous system has been little studied in research into the pathogenesis of goitre, and yet present-day knowledge of the close relations between the nervous system, the pituitary, and the thyroid compels us to acknowledge such an influence. We embarked upon a certain number of experiments to study what effects the central or peripheral nervous system might have on the action of goitrogenic substances. For this purpose we

sought to stimulate or inhibit these nerves by low-intensity electric shocks, decortication, interruption of the sympathetic or parasympathetic supply to the thyroid, blocking of the sensory receptors in the thyroid by Novocaine or irritation of these receptors by injections of rubber or substances like chloralose and chlorpromazine.

Goitre caused by a diet rich in cabbage

In 1928 Chesney, Clawson & Webster [6] observed that rabbits fed on cabbage developed goitre even when they were given an adequate amount of iodine The same phenomenon has been observed in guinea-pigs and rats

Our observations in the endemic areas of the People's Republic of Romania have shown that a diet excessively rich in cabbage must be considered as an aggravating factor in endemic goitre and is undoubtedly the cause of sporadic goitre in individuals consuming cabbage over long periods of the year.[21]

Medvedeeva,[16] Kabac,[14] and Greer & Astwood [13] have also demonstrated the role of the cyanides found in cabbages and other Cruciferae [13] in the production of endemic goitre

We set out to produce this type of experimental goitre while altering CNS function in the experimental animals Male rats weighing from 100 g to 130 g were placed on a diet containing 50% of cabbage for a period of 50 days. One batch on this diet was submitted to electric shocks from an 8-volt faradic current with sound-conditioned reflexes, and kept in a cage constructed so as to produce an experimental neurosis [27] Another batch on the same diet was given daily for 45 days intraperitoneal injections of 1% chloralose solution designed to cause drug inhibition of nervous function

By excitation or inhibition of nervous function in this way we were able to alter the intensity of the process of goitre formation initiated by a diet rich in cabbage The alterations were manifested in the following way by comparison with the control rats the weight of the thyroid in the rats fed with cabbage increased by 46 3%, in the rats with experimentally induced neurosis the weight increase was 65%; and in the rats given chloralose the increase was 36 3% At the end of the experiment, the basal metabolic rate of the rats fed on cabbage was unchanged, in the rats with a neurosis it had gone up by 19 8%, and in the rats on chloralose it had gone down by 6 5%

Histological examination demonstrated structural differences in the thyroid between these three groups of animals. By comparison with the controls we found the usual changes in the thyroid of the rats fed with cabbage, but in the rats in which a neurosis had been induced microfollicular hyperplasia occurred, with columnar cells, colloid, and areas of colloid re-absorption. In rats treated with chloralose, however, we found a decline in the intensity of the process of goitre formation.

The lesions of endemic goitre are very polymorphic, and develop slowly and continuously. First to appear are the lesions found in parenchymatous colloid goitre; then the lesions of nodular goitre develop, and finally those of degenerative fibrous conditions of the thyroid. While the first stages of this process are explicable in terms of stimulation by TSH caused by lack of iodine, the occurrence of the subsequent stages is less easy to understand. It may be assumed that thyroid antibodies are involved, and are able to aggravate the initial goitrogenic lesions

From the beginning of our research we have accepted the iodine deficiency theory—the theory that iodine deficiency is an essential factor in the production of goitre, whatever the exact process culminating in the goitre We have hardly touched on the agents responsible for iodine deficiency, studying rather the endogenous factors involved in an increased or decreased response of the thyroid to an inadequate supply of iodine. From this standpoint we have taken a very wide view of the problem, being ready to regard any factor at all as capable of affecting iodine metabolism and especially of preventing iodine from being taken up by the gland or taking part in hormone synthesis Our research work has been spread over nearly ten years and carried out in the face of many vicissitudes—hence its incompleteness.

Our results make a small contribution to knowledge of experimental goitre. Goitre has been produced experimentally by a diet rich in cabbage,[6] by a diet poor in iodine,[15] by sulfaguanidine,[17] and by thiouracil[5] We have used these different experimental methods to produce goitres in rabbits, guinea-pigs, and rats, but we also studied the effects of variations of neural or hormonal function and of auto- or iso-immunization The results in some cases were unexpected and difficult to interpret—for instance, with the long-term changes in the level of iodine in the blood, in oxygen consumption, and in iodine uptake after injection of Novocaine or rubber into the thyroid These results throw some light on the unfavourable effects of sclerotic lesions in the thyroid, which behave, in fact, as inclusion bodies. Our most recent studies are on the relationships between the pathology of thyroid immunization and the development of deficiency or drug-induced goitre. As in the other experimental fields, our results raise more problems than they solve.

Influence of the Central Nervous System on Experimental Goitre

The influence of the nervous system has been little studied in research into the pathogenesis of goitre, and yet present-day knowledge of the close relations between the nervous system, the pituitary, and the thyroid compels

sought to stimulate or inhibit these nerves by low-intensity electric shocks, decortication, interruption of the sympathetic or parasympathetic supply to the thyroid, blocking of the sensory receptors in the thyroid by Novocaine or irritation of these receptors by injections of rubber or substances like chloralose and chlorpromazine

Goitre caused by a diet rich in cabbage

In 1928 Chesney, Clawson & Webster[6] observed that rabbits fed on cabbage developed goitre even when they were given an adequate amount of iodine. The same phenomenon has been observed in guinea-pigs and rats

Our observations in the endemic areas of the People's Republic of Romania have shown that a diet excessively rich in cabbage must be considered as an aggravating factor in endemic goitre and is undoubtedly the cause of sporadic goitre in individuals consuming cabbage over long periods of the year.[21]

Medvedeva,[18] Kabac,[14] and Greer & Astwood [13] have also demonstrated the role of the cyanides found in cabbages and other Cruciferae [13] in the production of endemic goitre.

We set out to produce this type of experimental goitre while altering CNS function in the experimental animals Male rats weighing from 100 g to 130 g were placed on a diet containing 50% of cabbage for a period of 50 days One batch on this diet was submitted to electric shocks from an 8-volt faradic current with sound-conditioned reflexes, and kept in a cage constructed so as to produce an experimental neurosis [27] Another batch on the same diet was given daily for 45 days intraperitoneal injections of 1% chloralose solution designed to cause drug inhibition of nervous function.

By excitation or inhibition of nervous function in this way we were able to alter the intensity of the process of goitre formation initiated by a diet rich in cabbage The alterations were manifested in the following way: by comparison with the control rats the weight of the thyroid in the rats fed with cabbage increased by 46 3%, in the rats with experimentally induced neurosis the weight increase was 65%; and in the rats given chloralose the increase was 36 3% At the end of the experiment, the basal metabolic rate of the rats fed on cabbage was unchanged, in the rats with a neurosis it had gone up by 19 8%, and in the rats on chloralose it had gone down by 6.5%

Histological examination demonstrated structural differences in the thyroid between these three groups of animals. By comparison with the controls we found the usual changes in the thyroid of the rats fed with cabbage, but in the rats in which a neurosis had been induced microfollicular hyperplasia occurred, with columnar cells, colloid, and areas of colloid re-absorption In rats treated with chloralose, however, we found a decline in the intensity of the process of goitre formation.

Goitre induced by methylthiouracil

In another series of experiments we studied the effects of decortication or neurosis induced by electric shock on goitre caused by methylthiouracil. We used male rats weighing 73 g to 130 g; administered 15 mg of methylthiouracil daily for 3 weeks to one batch; carried out decortication by cauterization 10-12 days before the administration of methylthiouracil in another; and submitted a third group that had already received methylthiouracil to daily electric shocks [32]

At the end of the experiment, the thyroids and pituitaries were excised and implanted in tadpoles in accordance with the Voitkevici-Kabak technique.[14, 45] With this method the length of the tadpole's intestine diminishes in proportion to the amount of metamorphogenic substances in the implant, i.e., in proportion to the amount of TSH or thyroid hormone.

Our results (Table I) show that neither decortication alone nor electroshock affects the weight of the thyroid in rats If methylthiouracil is administered at the same time, however, the goitre produced is very slight, and the hormone content of the gland and the amount of TSH show little change.

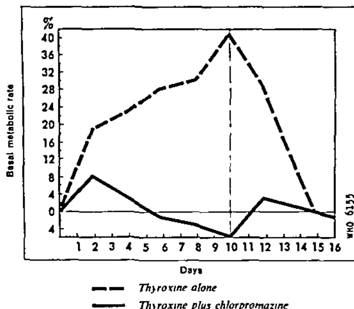
TABLE I WEIGHT AND HORMONE CHANGES IN THE THYROID AND PITUITARY GLANDS OF THE RAT AFTER ADMINISTRATION OF METHYLTHIOURACIL AND AFTER DECORTICATION

Batch	Weight of thyroid in mg	Weight of pituitary in mg	Reduction in length of tadpole intestine (%)*	
			after implantation of thyroid	after implantation of pituitary
Controls	9 4	4 33	13 4	46 6
Methylthiouracil only	26 7	4 81	26 8	49 4
Decortication only	9 9	4 16	13 4	46 8
Decortication plus methylthiouracil	13 8	4 35	27 8	44 3
Electroshock only	10 2	4 62	15 2	45 2
Electroshock plus methylthiouracil	17 8	5 01	19 9	47 6

Action of chlorpromazine

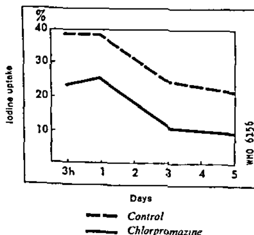
In order to elucidate the part played by the CNS, we decided to investigate the effect of chlorpromazine. In a study of the range of action of chlorpromazine in clinical and experimental hyperthyroidism we had observed that it lessens thyroid uptake of ^{131}I and reduces the calorific action of thyroxine to nil.[31] We therefore administered to one batch of rats

FIG. 1. EFFECT OF CHLORPROMAZINE ON THE ACTION OF THYROXINE



0 10 mg of thyroxine every other day for 10 days, and to another the same amount of thyroxine on alternate days plus 1 mg of chlorpromazine intraperitoneally every day for 10 days. We studied the basal metabolic rate till it returned to normal The oxygen consumption chart shows that chlorpromazine reduces the action of thyroxine on the tissues (Fig. 1)

FIG 2. INFLUENCE OF CHLORPROMAZINE ON IODINE UPTAKE



Four hours after the administration of the 1 mg of chlorpromazine, 0 84 μc of ^{131}I was injected, and 4 hours after this the iodine uptake was determined. We continued to give chlorpromazine for 5 days, twelve-hourly for the first two days, every 24 hours for the last three Fig 2 shows that iodine uptake was invariably 10% to 15% less than in the control animals

All these experiments proved that variation in CNS function influences the iodine uptake of the thyroid

Goitre induced by methylthiouracil

In another series of experiments we studied the effects of decortication or neurosis induced by electric shock on goitre caused by methylthiouracil. We used male rats weighing 73 g to 130 g; administered 15 mg of methylthiouracil daily for 3 weeks to one batch; carried out decortication by cauterization 10-12 days before the administration of *methylthiouracil in* another; and submitted a third group that had already received methylthiouracil to daily electric shocks[32]

At the end of the experiment, the thyroids and pituitaries were excised and implanted in tadpoles in accordance with the Voitkevici-Kabak technique.[11, 45] With this method the length of the tadpole's intestine diminishes in proportion to the amount of metamorphogenic substances in the implant, i e., in proportion to the amount of TSH or thyroid hormone.

Our results (Table I) show that neither decortication alone nor electroshock affects the weight of the thyroid in rats. If methylthiouracil is administered *at the same time, however, the goitre produced is very slight, and* the hormone content of the gland and the amount of TSH show little change.

TABLE I WEIGHT AND HORMONE CHANGES IN THE THYROID AND PITUITARY GLANDS OF THE RAT AFTER ADMINISTRATION OF METHYLTHIOURACIL AND AFTER DECORTICATION

Batch	Weight of thyroid in mg	Weight of pituitary in mg	Reduction in length of tadpole intestine (%).	
			after implantation of thyroid	after implantation of pituitary
Controls	9 4	4.33	13 4	45 6
Methylthiouracil only	26 7	4 81	26 8	49 4
Decortication only	9 9	4 16	13 4	46 6
Decortication plus methylthiouracil	13 8	4 35	27 8	44.3
Electroshock only	10 2	4 62	15 2	45 2
Electroshock plus methylthiouracil	17 8	5 01	19 9	47 6

Action of chlorpromazine

In order to elucidate the part played by the CNS, we decided to investigate the effect of chlorpromazine. In a study of the range of action of *chlorpromazine in clinical* and experimental hyperthyroidism we had observed that it lessens thyroid uptake of ^{131}I and reduces the calorific action of thyroxine to nil.[34] We therefore administered to one batch of rats

Cervical sympathectomy had various effects on thiouracil-induced goitre. Our experiments were carried out on 20 male rabbits whose weight varied between 1400 g and 2000 g. One batch of 10 received 0 05 g of methylthiouracil daily for 21 days, another received the same amount of methylthiouracil after a right unilateral sympathectomy At the end of the experiment, both batches and a batch of controls were killed We found that under the influence of methylthiouracil the thyroid had generally tripled in size, but that in the animals which had had the unilateral sympathectomy as well there was much less hypertrophy, particularly in the right lobe. The changes in the ratio of thyroid to body weight were very characteristic, as shown in Table II

TABLE II WEIGHT CHANGES IN THE THYROID OF RABBITS AFTER SYMPATHECTOMY AND ADMINISTRATION OF METHYLTHIOURACIL

Batch	Average weight of thyroid (mg)	Weight of thyroid per 100 g body weight (mg)
Controls	82 6	5 80
Sympathectomy only	97 9	7 20
Methylthiouracil only	383 3	21 10
Methylthiouracil plus sympathectomy	201 4	11 50

These experiments prove that methylthiouracil-induced goitre is modified by the cervical sympathetic outflow The difference in weight between the right and the left lobes confirms this finding.

Histological examination of the thyroid showed characteristic changes in sympathectomized animals given methylthiouracil Whereas in rabbits on methylthiouracil only we found the well-known picture of cellular hyperplasia, with disappearance of colloid, appearance of mitoses, and marked hyperaemia, in sympathectomized animals there was very little hyperplasia of the follicular cells, the tissue structure approximating to normal The mitoses were in process of disappearing, and colloid was visible in abundance (Fig 4)

We observed also that these structural changes appear both in the lobe on the side of the sympathectomy and in the contralateral lobe, a finding that indicates a reflex action mediated via the pituitary

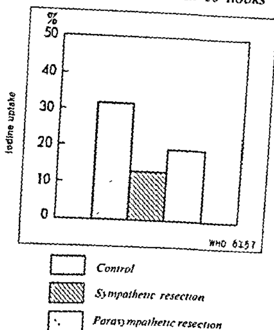
These changes taken as a whole demonstrate that sympathectomy reduces the goitrogenic effect of methylthiouracil and produces a goitre of mixed type, with colloid present, whereas methylthiouracil alone produces a parenchymatous goitre (Table III)

and also the intensity of action of goitrogenic factors. We believe that, subject to certain reservations, the same phenomena may occur in man. This view is supported by the appearance and rapid development of goitre in individuals subjected to stress, and of hyperthyroidism or neoplastic changes secondary to CNS hyperfunction. The findings also agree with those of Amiragova[2] who made intricate studies on the influence of states of CNS excitation, inhibition, or neurosis on thyroid uptake of ^{131}I and the blood level of PBI

Influence of the Autonomic Nervous System on the Production of Goitre

A question we asked ourselves was whether the peripheral nerves of the autonomic system in the thyroid had any effect on the process of goitre formation To answer this question, we embarked upon three series of experiments: (a) study of iodine uptake after denervation of the gland and blocking of nerve impulses with Novocaine, (b) parasympathetic denervation and subsequent modification of the goitre with methylthiouracil;[29] (c) blocking of the nerve impulses in the thyroid with Novocaine and subsequent study of iodine uptake and the basal metabolic rate;[22, 31, 46, 47] (d) as (c), but substituting infiltration with rubber for blocking with Novocaine.[20]

FIG 3 INFLUENCE OF SYMPATHETIC AND PARASYMPATHETIC RESECTION ON IODINE UPTAKE AFTER 30 HOURS



The first series of experiments was carried out on 26 adult rabbits, which were given 1 8 μc of ^{131}I intraperitoneally after cervical sympathectomy or section of the laryngeal nerves. Measurement of radioactivity was done 3, 30 and 48 hours after administration of the radioactive iodine. We found that resection of the sympathetic or of the parasympathetic nerves reduces iodine uptake, the more marked effect being produced by sympathetic denervation (Fig. 3) It is of interest to note that after parasympathetic denervation the ratio of the weight of the thyroid to that of the body increased by 18 6%.

TABLE III. HISTOLOGICAL CHANGES IN THE THYROID OF RABBITS AFTER TREATMENT WITH METHYLTHIOURACIL AND AFTER CERVICAL SYMPATHECTOMY

Batch	Diameter of follicles	Height of cells	Colloid	Mitoses per 100 follicles
Controls	36 9	3 7	Present, with vacuoles	0.5
Right sympathectomy only	43.1	5 6	Present, with vacuoles	0 75
Methylthiouracil only	55 4	14.8	Absent	24 00
Methylthiouracil plus sympathectomy	30.8	5 6	Present, with vacuoles	3 00

These histological findings are explained by the fact that the administration of methylthiouracil is usually associated with a decreased TSH secretion which slows down the thyroid response.

Histological examination of the pituitary revealed an increase in the number of basophils and a decrease (to the point of disappearance) of the eosinophils in animals treated with methylthiouracil only, both these phenomena being less marked in sympathectomized animals (Table IV).[24]

TABLE IV CYTOLOGICAL CHANGES IN THE PITUITARY OF RABBITS AFTER TREATMENT WITH METHYLTHIOURACIL AND AFTER CERVICAL SYMPATHECTOMY

Batch	Chromophobes %	Eosinophils %	Basophils %
Controls	45-55	30-35	10-15
Sympathectomy only	50-60	10-15	25-30
Methylthiouracil only	35-45	—	55-65
Methylthiouracil plus sympathectomy	50-55	1-3	40-50

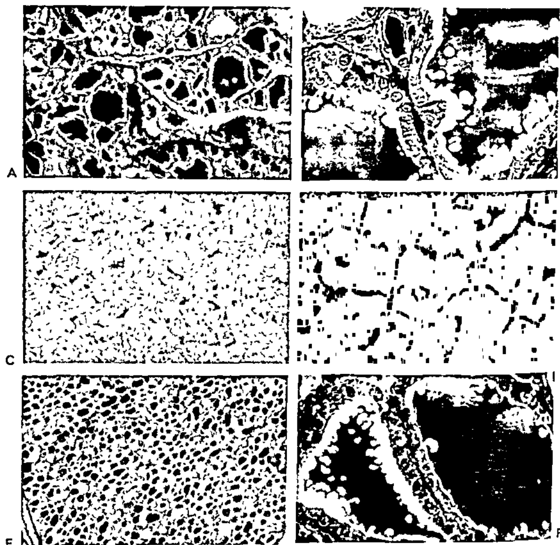
These findings agree with research results showing that sympathectomy lessens thyroid response to exogenous TSH in experimental animals. *It is therefore probable that variation in autonomic tone partly explains individual variability of response to goitrogenic factors; this variability is found in endemic areas.* In his monograph on thyroid conditions Danielopolu has maintained the view that persons with colloid goitre suffer from vagotonia.[8]

Influence of Nerves within the Thyroid

Changes in iodine uptake after intrathyroid injection of Novocaine

To determine the role of nerves within the thyroid in the appearance and development of goitre, we studied the changes in basal metabolism, in the

FIG. 4 CHANGES IN THE THYROID IN THE RABBIT AFTER CERVICAL SYMPATHECTOMY AND METHYLTHIOURACIL



A *and* B *Cervical sympathectomy (A×60, B×180)*
C *and* D *Methylthiouracil (C×60, D×180)*
E *and* F: *Methylthiouracil plus cervical sympathectomy (E×60, F×180)*

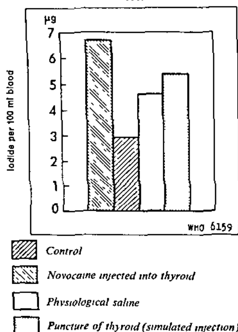
TABLE V RADIOACTIVITY OF FRESH RABBIT THYROID EXTRACT AFTER INFILTRATION OF THYROID WITH NOVOCAINE

Batch of animals	Radioactivity* per mg of extirpated thyroid		
	after 6 hours	after 12 hours	after 24 hours
Control	47 ±2.1	60.5±2.7	92.9±4.1
Injected with Novocaine	38 ±1.6	45.2±2.1	59.4±2.4
Injected with physiological saline	51.1±2.2	61.5±2.7	85.0±3.8

* Expressed in counts per minute by Geiger-Müller counter

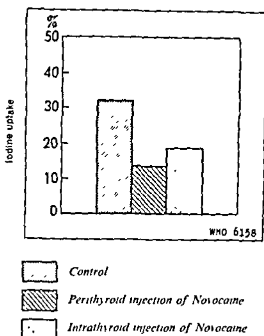
Injection of Novocaine into the thyroid is also followed by changes in the blood-iodide level and in basal metabolism. The iodide level was measured in 32 male rats weighing between 180 g and 220 g, before and after two intrathyroid injections of 0.1 ml of Novocaine in 0.4% solution, given at 9 days' interval. One batch of animals received physiological saline instead of Novocaine, another had a needle inserted into their thyroids without an injection being given, and a third batch served as controls. The rats were killed 9-13 days after the last injection [31]. In the animals that had received Novocaine injections we observed a blood-iodide level varying from 2.2 to 3.7 μg per 100 ml (average 2.9 μg per 100 ml), this level was 56.8% less than the level in the controls, which varied from 6.5 to 7.1 μg per ml (average 6.7 μg per 100 ml) (Fig. 6).

FIG. 6 CHANGE IN BLOOD-IODIDE LEVEL OF RAT AFTER INJECTION OF NOVOCAINE INTO THYROID



It is of interest to note that the iodide level in animals receiving physiological saline was 31.4% less than in the controls, and that in

FIG. 5. INFLUENCE OF NOVOCAINE INJECTED INTO AND AROUND THE THYROID ON IODINE UPTAKE



uptake of radioactive iodine, in blood-iodide level, and in tissue structure produced by injection of Novocaine into the thyroids of adult male rabbits and rats. Under conditions similar to those of our experiments on the effects of cervical sympathectomy, we injected a 0.5% solution of Novocaine into the parathyroids and thyroids of rabbits and measured thyroid uptake of radioactive iodine after the animals had been given 50 μc of ^{131}I intraperitoneally.[21] In these conditions iodine uptake was 13.1% 24 hours after perithyroid injection of Novocaine, 18.4% after intrathyroid injection, and 32.2% in the control group (Fig. 5).

In another series of experiments, we studied the uptake of radioactive iodine in rabbits after injection of 0.1 ml of Novocaine in 0.4% solution into the thyroid lobes. For comparison, we examined the effects of physiological saline injected under the same conditions. Sixteen days after this infiltration of the thyroid with Novocaine we injected 50 μc of radioactive iodine intraperitoneally.[28] Extirpating the thyroids, we measured their radioactivity with a Geiger-Müller counter at the end of 6, 12, and 24 hours. We found that at the end of 6 hours the radioactivity per mg of thyroid tissue was 18.9% less than in the controls, at the end of 12 hours 20.3% less, and at the end of 24 hours 38.2% less (Table V).

In animals that had received intrathyroid injections of physiological saline changes in iodine uptake were minimal and of no real significance; compared with the controls the uptake was increased by only 8.4% at the end of 6 hours and 1.6% at the end of 12 hours, while it was decreased by 8.5% at the end of 24 hours.

Sixteen days after the intrathyroid injection of Novocaine the iodine uptake rate was still less than that of the controls. It is a matter for speculation whether this is due to lasting reflex changes or to lesions of the nerve endings caused by the Novocaine.

Changed response of the thyroid to TSH and decreased secretion of TSH

The changes occurring after the injection of Novocaine into the thyroid could be due either to decreased secretion of TSH or to lowered thyroid response to it. To study this, Vrabiescu et al.[47] injected 10 I.U of TSH per kg of body weight into guinea-pigs that had received an injection of Novocaine into the thyroid 14 days earlier They found no significant change in oxygen consumption and no change in the structure of the thyroid tissue. It should however be observed that the amount of TSH used was very small and was injected a fairly long time after the Novocaine The findings in this experiment should therefore be treated with reserve, for it may be conjectured that the main change in the response to TSH occurs just after the injection of Novocaine.

We established one significant fact, that the disappearance of acetylcholine from the thyroid after injection of Novocaine still persists 14 days after the injection (Table VI)

TABLE VI CHANGES IN THE ACETYLCHOLINE CONTENT OF THE THYROID 14 DAYS AFTER ADMINISTRATION OF NOVOCAINE AND TSH

Batch	Number of animals	Total acetylcholine (μg per g of thyroid)
Controls	20	0 09±0 03
Novocaine (injected into the thyroid)	16	—
TSH (10 I U /kg body weight)	15	1 28±0 15
Novocaine plus TSH (10 I U /kg body weight)	13	1 09±0 1

The estimation of free and fixed acetylcholine was carried out on the abdominal muscle of the frog in accordance with the technique used in the Institute of Endocrinology, Bucarest.[41] The increase of acetylcholine in the thyroid after administration of TSH and its disappearance after injection of Novocaine show that Novocaine exercises a non-specific action upon the thyroid.

That Novocaine injected into the thyroid has a reflex action exerted not only locally but also at a distance is proved by the variation in the amount of TSH in the pituitary This is demonstrated by the following experiment in which we injected 0 1 ml of Novocaine in 0 4% solution into the thyroids of 46 adult rats weighing between 170 g and 200 g We injected the same amount of physiological saline into a control group. One batch of animals

those into whose thyroids a needle was inserted but no injection made the level was 19.4% less.

These findings prove not only that Novocaine has an effect as a chemical substance but also that there is a reflex mechanism originating within the thyroid itself.

Additional evidence for the role of neural function within the thyroid is furnished by changes in the basal metabolism of guinea-pigs and rats after intrathyroid injection of Novocaine.[24] We infiltrated either one or both of the lobes with 0.1 ml of Novocaine in 0.2%-0.4% solution. Some animals received one injection, others two or three. Control animals were given an intramuscular injection of Novocaine and an intrathyroid injection of physiological saline The basal metabolic rate was measured at the beginning of the experiment, then 2, 24 and 72 hours afterwards, then every 3 or 4 days for 27 to 74 days

We found that after a latent period of at least 2-3 days the drop in the basal metabolic rate was between 9.9% and 30.3% in the guinea-pig and between 14 4% and 28% in the rat. The lowest figures were reached in 9 to 21 days in the guinea-pig and in 6 to 14 days in the rat; in the majority of cases the basal metabolic rate the returned to its initial value. The fall occurred even when the Novocaine was injected into only one lobe, and was the more marked in proportion as the amount of oxygen consumed at the beginning of the experiment was raised. Intramuscular injection of Novocaine and intrathyroid injection of physiological saline did not alter the oxygen consumption

During the experiment we also observed a slowing down, or even complete arrest, in the growth of the animals receiving Novocaine For a period of 7-14 days after the infiltration the animals displayed somnolence and bradykinesia. We noted, too, that infiltration of the thyroid with 1%, 2% or 4% Novocaine was in most cases followed by the death of the animals from cardiac and respiratory arrest, whereas intracardiac injection of the same doses was well tolerated.

The effects observed after injection of Novocaine into the thyroid reveal the importance of the perifollicular and vascular nerve endings in thyroid physiology and the part they play in pathological processes in the gland. Recent research into the density of this network of nerve fibres and their possible functions lends weight to this view.[4, 38]

Clinical observations at thyroidectomies on human beings in whom the thyroid and the surrounding tissues were infiltrated with Novocaine show that the changes in cardiac function and blood pressure usually found in operations on the thyroid are slight or even absent.[2] It would therefore be tempting to conclude that Novocaine injected into the gland acts only by setting off a reflex in the gland, since the effects of the injection are delayed and persist for a long time after the anaesthetic effect of the Novocaine has ended.

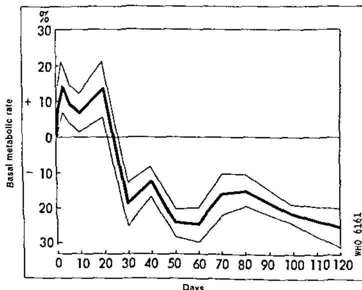
endings in the thyroid modify the secretion of TSH, the amount of the cholinergic agents, and sensitivity to TSH. It is, of course, possible that Novocaine acts as a stress agent

Action of inert substances on nerve endings in the thyroid

It is possible that nerve endings in the thyroid play a part in the appearance and development of goitres in which the thyroid lesions are very localized, as in lobar goitre, the solitary nodule, and nodular goitre We therefore tried to produce a lesion that would cause constant local irritation of the nerve endings After many trials, we hit upon the injection of a rubber solution (0 1 ml) into one of the lobes of the thyroid. Then we checked oxygen consumption, the iodide level in the blood, the iodine uptake, and structural changes in the thyroid tissue. The basal metabolic rate was measured at the end of 1, 3, and 6 days, then every 10 days for a period of 3 months.[20]

For the first 20 days the basal metabolic rate rose on the average by 14 5% then fell rapidly and remained at a low level The lowest it reached was —24 8% (Fig 8)

FIG 8 CHANGES IN BASAL METABOLIC RATE AFTER INJECTION OF RUBBER INTO LEFT THYROID LOBE OF RAT

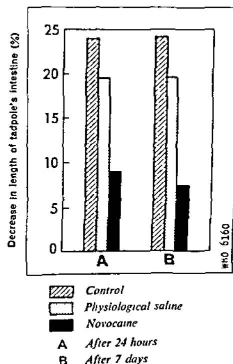


The iodide level, which was on the average 4.7 μg per 100 ml of plasma in the controls, was only 3 8 μg 6 days after the rubber was injected, 3 3 μg 18 days after, and 2 2 μg 44 days after (Fig 9)

were killed twenty-four hours after the injection of Novocaine and another 7 days later Using the technique of Voitkevici & Kabak, [11, 45] whereby metamorphogenic substances are estimated according to the reduction in length of tadpoles' intestines, we implanted 1 mg of pituitary taken from the experimental animals into tadpoles The reduction in length of the intestine was 22% for pituitary from the controls, and 8 9% after 24 hours (7.3% after 8 days) for pituitary from the animals injected with Novocaine (Fig 7) This shows that there is a drop in the concentration of TSH in the pituitary of rats given intrathyroid Novocaine. Implantation of 1 mg of thyroid under the same conditions showed that the metamorphogenic power of the thyroid was slightly less in the treated animals than in the controls This fall in the functional capacity of the thyroid secondary to the fall in the amount of TSH in the pituitary was also manifested by the drop in oxygen consumption, in iodine uptake, and in iodide level.

But not all of the various controlling hormones of the pituitary are reduced in amount Our experiments on pituitary uptake of ^{32}P showed that it increases by 29% in animals given intrathyroid injections of 0.1 ml of Novocaine in 0 4% solution 8 days before, whereas it is unchanged in animals injected with a similar volume of physiological saline. This indicates that Novocaine *acts differently on the various* pituitary hormones.[28]

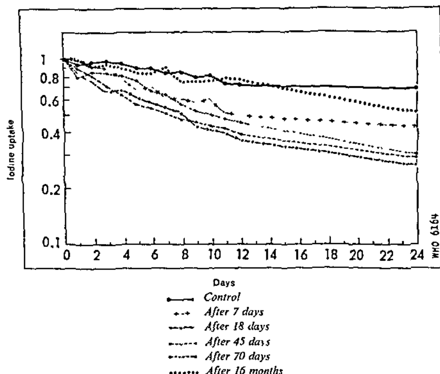
FIG 7 DECREASED METAMORPHOGENIC POWER OF PITUITARY UNDER INFLUENCE OF NOVOCAINE INJECTED INTO THYROID



There seems to be reason to assume that the initial action of Novocaine is on corticotrophin Study of phosphorus uptake by the adrenals under the same experimental conditions showed that after injection of Novocaine *into the thyroid* the uptake of ^{32}P may increase by 100% over that in control animals Injection of physiological saline causes an increase of only 23% [28]

All this research into the role of the nerve endings in thyroid function gives rise to the supposition that any factor modifying their morphological and functional integrity may also affect thyroid response to exogenous and endogenous factors. It also shows that the nerve

FIG. 10 CHANGES IN IODINE UPTAKE BY THE THYROID AFTER INJECTION OF RUBBER INTO THE LEFT THYROID LOBE OF THE RAT

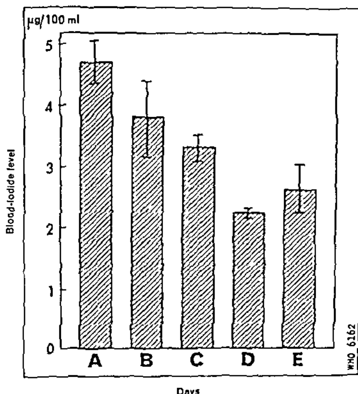


rubber was injected into the intact lobe. In rats, after subtotal extirpation of the left lobe, followed by injection of 0.1 ml of rubber solution into the right lobe, compensatory hypertrophy of the right lobe was very slight: 5 7% as compared with 53 1% in animals which did not receive injections of rubber This phenomenon resembles that which we observed in goitre induced by methylthiouracil Here the hypertrophy of the remaining lobe may reach 219 3%, but if rubber has been injected the hypertrophy is only 78 8% (Table VII)

Role of the Endocrine System in Experimental Goitre

In our studies of the production of experimental goitre we considered whether hypertrophy and hyperplasia were confined to the thyroid alone Given the glandular interrelationships that characterize the endocrine system, it seemed reasonable to assume that other glands were also implicated We therefore studied weight changes in the pituitary and thyroid and the action of certain hormones in experimental goitre induced by an iodine-poor diet and by methylthiouracil

FIG 9 CHANGES IN BLOOD-IODIDE LEVEL AFTER INJECTION OF RUBBER INTO THE LEFT THYROID LOBE OF THE RAT *



* The arrows show twice the statistical error

A *Control*
B *After 7 days*
C *After 20 days*
D *After 45 days*
E *After 70 days*

The uptake of ^{131}I by the thyroid and its level in the blood were measured after intraperitoneal injection of 2 μc of radioactive iodine. The estimations were carried out both *in vivo* and on animals killed at varying intervals Iodine uptake fell significantly between the 14th and 70th days after the injection of rubber (Fig. 10)

[illegible] lobe (into which the rubber [illegible] njection revealed a decrease [illegible] ease in colloid. It may be assumed that the injected rubber leads to reflex inhibition of the secretion of TSH or reduced sensitivity of the thyroid to this hormone (Fig 11)

This assumption was confirmed, for the compensatory hypertrophy of one lobe that usually follows extirpation of the other did not occur when

TABLE VII COMPENSATORY HYPERTROPHY OF THE CONTRALATERAL LOBE AFTER SUBTOTAL THYROID LOBECTOMY IN NORMAL RATS AND IN RATS GIVEN METHYLTHIOURACIL OR INTRATHYROID RUBBER INJECTIONS

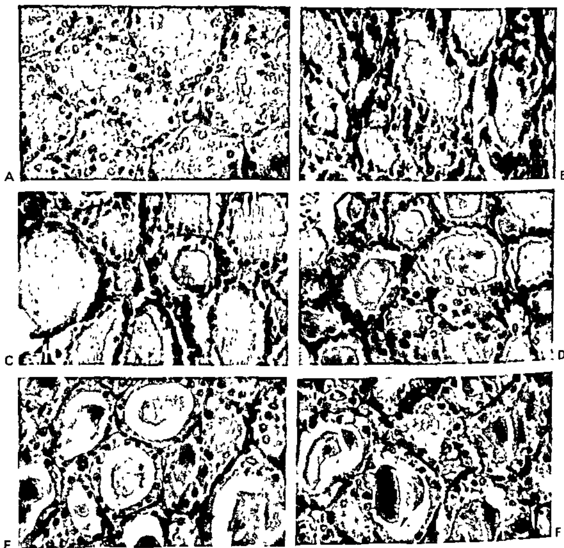
Batch	Number of rats	Average weight of right lobe (mg)	Weight increase by comparison with controls (%)
Controls	12	8 37±0 27	
Subtotal thyroid lobectomy (left lobe) only	10	12 82±0 51	53 1
Lobectomy plus rubber injections	10	8 85±0.25	5 7
Lobectomy after methylthiouracil	11	27.53±1 06	231 3
Lobectomy and rubber injections after methylthiouracil	10	14 97±0 92	78 8

A preliminary series of experiments were performed on batches of 4-5 month old ducks One of these batches was given water from an endemic area but lived in a non-endemic area, another received water from a non-endemic area but lived in an endemic area A diffuse parenchymatous goitre appeared in the ducks living in the endemic area at the end of 3 months, whether they received local water or water from a non-endemic area Towards the end of the experiment (after 7 months), this parenchymatous goitre developed into a colloid goitre

The weight of the thyroid in ducks that had received water from a non-endemic area but lived in an endemic area increased by 54 1%, whereas in ducks receiving local water it increased by 84 5% This shows the importance of water in the production of goitre, but also the role of other active goitrogenic factors in endemic areas As well as thyroid hypertrophy, we observed pituitary and adrenal hypertrophy in these ducks, but found no parallelism between the three glands in the intensity of the hyperplastic process (Table VIII)

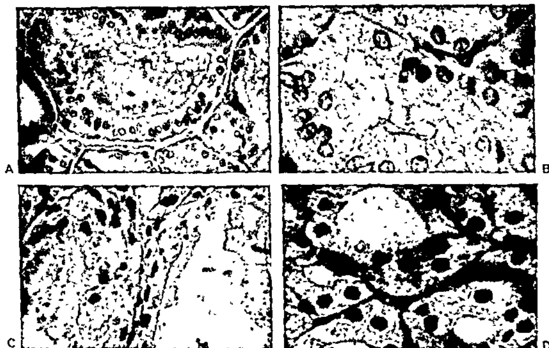
As can be seen, there is a correlation between the hypertrophy of the pituitary and that of the adrenals, but neither seems to be related to that of the thyroid It may be assumed that pituitary and adrenal hypertrophy is the manifestation of the adaptation of these glands to the goitrogenic conditions of the environment, and that these glands influence the goitrogenic process in a more complex way

FIG 11 CHANGES IN THYROID OF RAT AFTER INJECTION OF RUBBER INTO THE LEFT LOBE



A *Thyroid of control rat* (×150)
B *7 days after injection of rubber* (×150)
C [illegible] (×150)
D [illegible] (×150)
E [illegible]
F [illegible] (×150)

FIG 12. THE STRUCTURE OF IODINE-DEFICIENCY GOITRE



A *Thyroid of control rat* (× 150)
B *Rat thyroid, goitre from iodine-deficient diet (3 months), hypertrophic hyperplastic stage* (× 300)
C *Rat thyroid, goitre from iodine-deficient diet (7-9 months), exhaustion atrophy* (× 150)
D *Rat thyroid, goitre from iodine-deficient diet (12-13 months)* (× 300)

on thyroid hypertrophy and hyperplasia was different from that on basal metabolism—and sometimes the effect was in the opposite direction

The appearance of colloid in the follicles under the influence of the steroid hormones or extracts of the thymus or pineal glands proves that these substances hasten the development of parenchymatous goitre into colloid goitre or alternatively reduce the degree of epithelial hyperplasia. We used only a small dose of hormone in our studies, and it may be assumed that the effect of hormones on iodine-deficiency goitre varies with the dose given The greater frequency of goitre in women and, in both sexes, at puberty, and its uneven distribution in a community may be due to variations in the amounts of these hormones

Study of the uptake of ^{131}I in rats after administration of oestradiol shows that small doses of this hormone—0.1 mg—stimulate the uptake and large doses—10 mg—inhibit it (Fig 14)[33] It may therefore be assumed that in women suffering from iodine deficiency these same effects may result from hyper- or hypofolliculinaemia. Mention may be made of the most

TABLE VIII CORRELATION COEFFICIENTS BETWEEN THE WEIGHT OF THE PITUITARY, THE THYROID, AND THE ADRENAL GLANDS OF DUCKS ON A GOITROGENIC DIET

Glands compared	Correlation coefficient r (Bravais-Pearson)	Statistical significance
Pituitary/adrenals	+0 43 ± 0 10	Significant
Pituitary/thyroid	+0 28 ± 0 11	Not significant
Thyroid/adrenals	+0 24 ± 0 11	Not significant
Thickness of thyroid epithelium/thyroid hypertrophy	−0 39 ± 0 11	Not significant

It may also be assumed that hormones other than TSH play a part in goitre formation We administered steroid and protein hormones* to rats on an iodine-poor diet of starch, bean flour, cellulose wool, dry yeast, powdered bone, pure casein, animal fat, and sodium chloride. To this diet we added 10 drops of vitamins A and D weekly The iodine content of this diet is 4 μg per 100 g, and the daily consumption of iodine by each rat was approximately 0 5-0 6 μg At the end of 3 months this diet brought about a rise in the weight of the thyroid from the 15-16 mg of the controls to 48 mg. It also caused cell hypertrophy and epithelial hyperplasia, the cell height being 18-20 μ as against the 8-10 μ of the control animals. The epithelium presented a picture of microfollicular goitre without colloid (Fig. 12) Oxygen consumption was down, iodine uptake up.

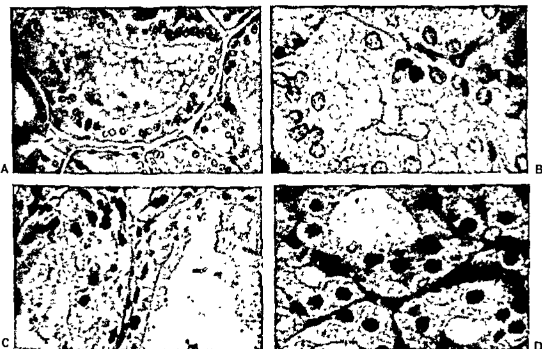
In a batch of animals on a similar diet, administration of 1 mg of cortisone thrice weekly reduced goitre formation markedly. The average weight of the thyroid was only 16 mg, and the height of the epithelial cells varied between 15 μ and 16 μ The follicles contained colloid.

The development of goitre was markedly diminished in other animals on the same iodine-poor diet by the administration thrice weekly for 4 months of 1 mg of desoxycorticosterone acetate (DOCA), or 0.1 mg of oestradiol benzoate, or 3 mg of testosterone, or 1 mg of ACTH, or pineal or thymus extract Injection of 5. I.U. of growth hormone (TSH) did not affect the height of the follicular cells, but reduced the hyperplasia (Table IX, Fig 13)

Except in the animals that received oestradiol, pineal extract, or TSH, oxygen consumption was little changed in comparison with the control animals on an iodine-poor diet only. Oestradiol and pineal extract reduced the basal metabolic rate, TSH increased it.[18] It is not without interest to observe that in iodine-deficiency goitre the influence of the hormones

* ACTH, TSH, thymus or pineal extract

FIG 12. THE STRUCTURE OF IODINE-DEFICIENCY GOITRE



A *Thyroid of control rat (×150)*
B *Rat thyroid, goitre from iodine-deficient diet (3 months), hypertrophic hyperplastic stage (×300)*
C *Rat thyroid, goitre from iodine-deficient diet (7-9 months), exhaustion atrophy (×150)*
D *Rat thyroid, goitre from iodine-deficient diet (12-13 months) (×300)*

on thyroid hypertrophy and hyperplasia was different from that on basal metabolism—and sometimes the effect was in the opposite direction

The appearance of colloid in the follicles under the influence of the steroid hormones or extracts of the thymus or pineal glands proves that these substances hasten the development of parenchymatous goitre into colloid goitre or alternatively reduce the degree of epithelial hyperplasia We used only a small dose of hormone in our studies, and it may be assumed that the effect of hormones on iodine-deficiency goitre varies with the dose given The greater frequency of goitre in women and, in both sexes, at puberty, and its uneven distribution in a community may be due to variations in the amounts of these hormones

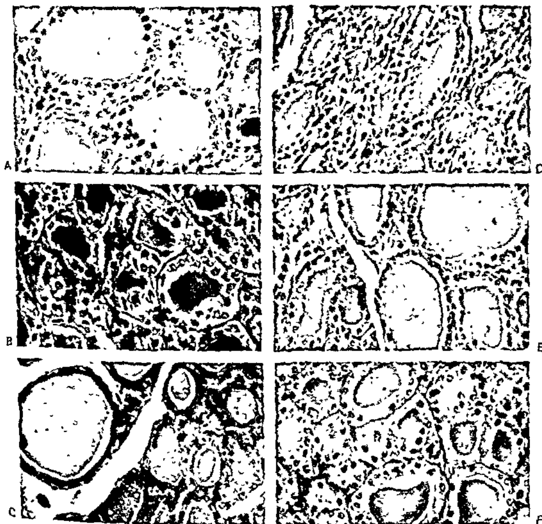
Study of the uptake of ^{131}I in rats after administration of oestradiol shows that small doses of this hormone—0.1 mg—stimulate the uptake and large doses—10 mg—inhibit it (Fig 14) [33] It may therefore be assumed that in women suffering from iodine deficiency these same effects may result from hyper- or hypofolliculinaemia. Mention may be made of the most

TABLE IX. CHANGES IN IODINE-DEFICIENCY GOITRE UNDER THE INFLUENCE OF DIFFERENT HORMONES

Batch	Number of rats	Weight of thyroid (mg)	Average height of cells (μ)	Colloid	Hyperplasia and hypertrophy	Basal metabolic rate (Cal/m²/hr)
Controls	10	14	9	normal	—	45.0 ± 0.75
Iodine-deficient diet	10	48	20	—	+++	41.18 ± 0.20 (0)
Iodine-deficient diet plus cortisone	10	16	14	+	±	42.50 ± 0.40 (+3.2 %)
Iodine-deficient diet plus desoxycorticosterone	10	15	12	++	±	43.20 ± 0.24 (+4.5 %)
Iodine-deficient diet plus oestradiol	10	16	8	+++	—	39.00 ± 0.45 (—6 %)
Iodine-deficient diet plus testosterone	10	13	12	+	+	40.00 ± 0.31 (—2.7 %)
Iodine-deficient diet plus ACTH	8	15	14	±	+	42.64 ± 0.38 (+3.4 %)
Iodine-deficient diet plus pineal extract	10	24	9	++	±	39.80 ± 0.52 (—5 %)
Iodine-deficient diet plus growth hormone	8	20	19	±	+	43.95 ± 0.62 (+7 %)
Iodine-deficient diet plus thymus extract	10	18	13	+	+	40.80 ± 0.46 (—1 %)
Iodine-deficient diet plus castration	10	14	9	±	±	41.70 ± 0.21 (+1.2 %)

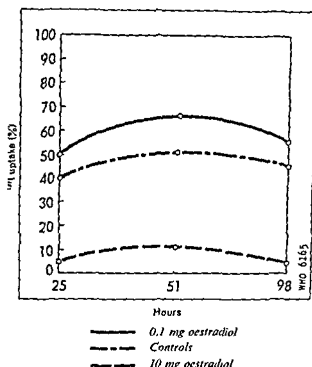
recent experiments along the same lines, on iodine uptake in the normal rat after administration of extract of the pineal gland. We injected 2 ml of this extract every 4 hours for 24-48 hours into albino rats weighing 100 g Four hours after the beginning of the experiment 40 μc of ^{131}I were injected intraperitoneally. The animals were then killed in successive batches, to begin with every 3 minutes after the injection, then every 2 hours

FIG 13. ACTION OF HORMONES ON IODINE-DEFICIENCY GOITRE



A *Control* (×150)
B *Iodine-deficient diet plus cortisone* (×150)
C *Iodine-deficient diet plus DOCA* (×150)
D *Iodine-deficient diet plus ACTH* (×150)
E *Iodine-deficient diet plus oestradiol* (×150)
F *Iodine-deficient diet plus pineal extract* (×150)

FIG 14 THYROID UPTAKE OF RADIOACTIVE IODINE AFTER TREATMENT WITH OESTRADIOL

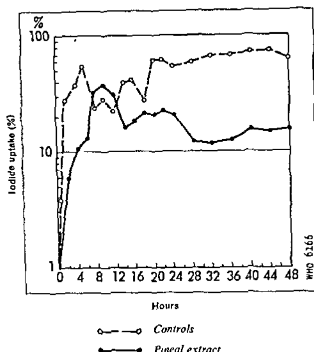


for 24 hours, then every 4 hours for the next 24. We were able to establish that pineal extract reduces iodine uptake (Fig. 15) [22]

In the relationships that exist between the process of goitre formation and the functional balance of the various endocrine glands, TSH has a special place. It is generally admitted that in iodine deficiency thyroid hypertrophy and hyperplasia occur under the influence of hypersecretion of TSH. Given the development of the goitrogenic process and of the degenerative changes that appear in the thyroid cells under the influence of iodine deficiency, the question may be asked what the response to TSH is during the development of a goitre in a thyroid deprived of iodine It must be assumed that, to begin with, microfollicular parenchymatous goitre is a manifestation of a still normal thyroid response to endogenous TSH, whereas the various forms of colloid goitre and the exhaustion states characteristic of the subsequent stages are indicative of lowered or even totally lacking thyroid response to TSH.

To elucidate this question we carried out certain experiments. We first measured the iodine uptake of rats on a normal diet. this we did by intraperitoneal injection of 1 8 μc of ^{131}I and found the uptake to be 38.5% In rats placed for 3 months on a diet deficient in iodine the uptake was

FIG 15. ACTION OF PINEAL EXTRACT ON IODINE UPTAKE BY THE THYROID



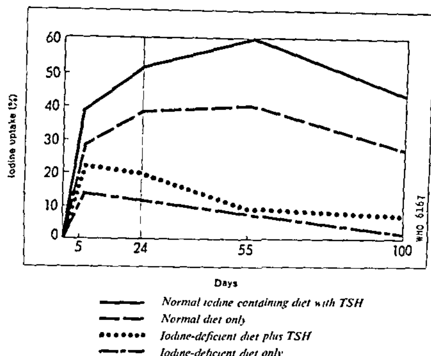
only 12% For comparison we injected TSH into rats on a normal diet and found the iodine uptake to be 52%, while in rats kept for 3 months on an iodine-deficient diet a similar injection increased the uptake to 23%. (Fig 16).[35]

Under similar experimental conditions the basal metabolic rate of rats on a normal diet rose after injection of TSH by 25%, but in rats on the iodine-deficient diet it rose by 7% only In animals on an iodine-deficient diet but not given TSH it fell by 5% (Fig 17)

These results show that iodine uptake is reduced by an iodine-deficient diet, even when the thyroid is stimulated by TSH Monney, Rall & Rawson [36] found an increase in iodine uptake in rats kept on a diet deficient in iodine, from 28 9% on the 10th to 42 3% on the 20th day In our experiments, however, we found a decrease in iodine uptake at the end of 3 months This difference is probably due to the fact that there is non-iodinated colloid that can take up the iodine for the first 20 days, but by the end of 3 months microfollicular hyperplasia has set in with a reduced amount of colloid and degenerative cell lesions

The change from parenchymatous goitre to a colloid goitre and then to a degenerated goitre may undoubtedly be explained by the unequal

FIG. 16 IODINE UPTAKE BY THYROID OF IODINE-DEFICIENT RAT AFTER ADMINISTRATION OF TSH



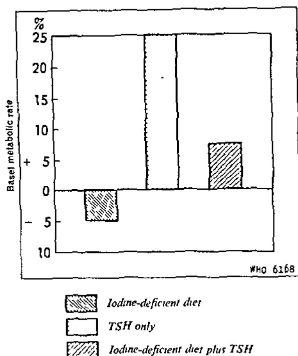
response of the thyroid to TSH as the process goes on. Taken in conjunction with the considerable variations in the secretion of TSH, it could provide a partial explanation for progressive changes that take place in the goitre. To these factors must be added auto-immunization, which may account for the occurrence of interstitial lesions in the form of infiltrations and for the trend towards sclerosis in old goitres

Role of Immunopathology of the Thyroid in Experimental Goitre

The recent research of Rose and Witebsky,[42, 48, 49] Doniach & Roitt,[10] and Gear [12] on the role of immunological auto-aggression in the pathology of the thyroid compels us to consider such a process as possible, at least during the later changes in the structure of a goitre

The thyroid contains thyroglobulin, which is known to have great antigenic powers, and a cell nucleoprotein complex that can display antigenic activity in some pathological states, either by the liberation of thyroglobulin into the circulation or by the release of substances from necrotic follicular or interfollicular cells. We set ourselves the task of finding out to what extent the immunopathology of the thyroid plays a part in the appearance

FIG. 17. BASAL METABOLIC RATE IN IODINE-DEFICIENT RATS BEFORE AND AFTER ADMINISTRATION OF TSH



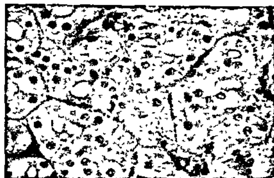
of goitre in animals brought up in normal living conditions, and in what way the antigen-antibody reaction may arise in the development of goitre—whether the goitre is produced by an iodine-deficient diet or by methylthiouracil

We were able to prove that immunopathology plays a part by inducing a hypoplastic microfollicular goitre in rabbits subjected to repeated iso-immunization A batch of male rabbits weighing about 2700 g were iso-immunized by a suspension of 100 mg of normal thyroid gland in Freund's adjuvant [a] The inoculation was repeated 4 times at intervals of 15 to 20 days One batch was killed 12 days after the last inoculation, another 90 days after In the blood of the first batch we found complement-fixing antibodies at a titre of 1/128-1/156, as well as precipitating antibodies The tissue changes were characteristic of immunity thyroiditis

The animals of the batch killed 90 days after the last inoculation had a hypertrophic, hyperplastic thyroid weighing nearly 4 times as much as normal (1 20 g)

[a] For the composition of Freund's adjuvant see Freund, J (1951) *Amer J clin Path*, 21, 645

FIG. 18 PARENCHYMATOUS GOITRE INDUCED IN RABBIT BY ISO-IMMUNIZATION



× 150

The structural characteristics of thyroid tissue under these experimental conditions were those of a microfollicular parenchymatous goitre (Fig 18)[41]

We did not go any further into the study of the hormonal characteristics of this immunity goitre. Its occurrence is probably due, however, to blocking of the process of thyroxine formation—a blocking whose mechanism we do not know—or to tissue uptake of the thyroid hormones, which would then stimulate an excessive secondary secretion of TSH and lead to the structural changes in the thyroid that are characteristic of the first stage of parenchymatous goitre. The blocking of the binding of iodine to protein by thyroid antigens could be accepted as the reason for this goitre.[36]

In another series of experiments we set out to study the antigenicity of goitre produced in animals by an iodine-deficient diet or by methylthiouracil[35] For this purpose we used a batch of 40 male rats weighing about 120 g, and immunized them either with their own thyroids or with those of rats of a homologous group. The thyroid tissue was emulsified in 20% physiological saline and incorporated into Freunds' adjuvant[a] in the proportion 1 part of tissue suspension to 3 parts of adjuvant. This suspension was injected intradermally in rats, either into the footpads or into the nape of the neck. The animals had previously received 25 mg of methylthiouracil for 20 days or been placed on an iodine-deficient diet (4 6 μg per 100 g of food) for 110 to 180 days. The methylthiouracil and the iodine-deficient diet were continued for the length of the immunization period (40 days).

Proof of the appearance of an experimental goitre under these conditions was afforded by the increase in the weight of the thyroid This increase, 12 mg only in the control animals, was as much as 40 mg in the animals on an iodine-deficient diet, and 60 mg in the animals on methylthiouracil. *Histological examination also revealed the usual changes in the tissues of* the thyroid.

In all the immunized animals the thyroid showed changes characteristic of immunity thyroiditis: scattered cytolysis of unequal intensity: fragmentation and disappearance of the nuclei of the follicular cells; interstitial infiltration with lymphocytes; rare plasma cells and eosinophils; and reduction of the amount of colloid, in some cases to the point of total disappearance (Fig 19).

FIG 19 CHANGES IN METHYLTHIOURACIL-INDUCED GOITRE IN THE RAT EFFECTED BY AUTO- AND ISO-IMMUNIZATION



A *Control* (×150)
B *Auto-immunization in the normal thyroid* (×150)
C *Methylthiouracil-induced goitre* (×150)
D *Methylthiouracil-induced goitre after iso-immunization with normal thyroid* (×150)

In animals immunized with thyroid from rats on an iodine-deficient diet or methylthiouracil, lesions appeared similar to, but less marked than those obtained in the aforementioned experiments Compared with the goitrogenic reaction obtained in non-immunized animals on an iodine-deficient diet or on methylthiouracil, the reaction in these animals was weaker, as shown by the thickness of the follicular epithelium—only 12 μ as against 18 μ in non-immunized rats The reduced response to thyroid antigen in animals on an iodine-deficient diet was thus proved

We found antibodies only in the blood of those animals that had received antigen in the form of thyroid tissue from iodine-deficiency goitre Their appearance was not constant, however, as was shown by the fact that complement was fixed in only 10 out of the 30 experimental animals and precipitating antibodies were present in only 14 (Table X). But the role of auto-immunization in the development of goitre cannot be disregarded merely because no circulating antibodies can be found. From the work of

TABLE X IMMUNOPATHOLOGICAL CHANGES IN THE GOITROUS THYROID

Batches of rats	No of animals	Goitrogenic factor	Duration of pre-treatment (days)	Duration of immunization (days)	Proportion of serological reactions (no. of animals)		Immunity lesions (no of animals)				Observations
					Complement-fixation reaction	Precipitating antibodies	Cytokaryolysis	Cell infiltrations	Colloid	Reticulo-endothelial system	
Goitre plus auto-immunization	5	Methyl-thiouracil	*110*	*30*	*1/5*	*2/5*	*3/5*	3/5	—	*3/5*	
Goitre plus iso-immunization by normal thyroid	5	Methyl-thiouracil	170	30	2/5	3/5	3/5	4/5	—	3/5	
Goitre plus auto-immunization	5	Iodine-deficient diet	110	30	—	—	2/5	3/5	2/5	3/5	
Goitre plus iso-immunization by normal thyroid	5	Iodine-deficient diet	170	45	4/5	5/5	2/5	3/5	—	2/5	
Control goitres	2	Methyl-thiouracil	170	30	—	1/2	—	—	—	—	Characteristic lesions
Control goitres	2	Iodine deficient diet	170	30	—	—	—	—	—	—	Characteristic lesions
Goitre plus unilateral thyroidectomy	1	Methyl-thiouracil	170	30	—	1/1	—	1/1	—	—	
Antithyroid auto-immunization	5	—	—	30	1/5	—	4/5	5/5	—	4/5	
Antithyroid iso-immunization	5	—	—	30	2/5	4/5	5/5	3/5	—	3/5	
Goitre auto-immunization plus TSH	5	Methyl-thiouracil	180	40	—	2/5	—	5/5	—	5/5	
Goitre auto-immunization plus cortisone	3	Methyl-thiouracil	180	40	1/5	1/5	2/5	1/5	—	1/5	

Witebsky et al it is known that the thyroid in dogs and guinea-pigs may present lesions due to the administration of homologous antigen without any antibodies appearing in the blood.[49] The reduced amount of thyroglobulin in the follicles, due to the initial hyperplastic process in the parenchyma, may explain the absence of serum antibodies as well as the finding of infiltration lesions in all these cases, pointing to the presence within the cells of an antibody undergoing rapid fixation

As in the other types of experimental goitre, it is possible that either hormones participating in the thyroid response or antibody-producing tissues play a part in the development of immunity conditions From this standpoint our research is only just beginning Nevertheless, we have established that TSH and cortisone influence the immunity reaction of the thyroid Thus the immunity condition of the rat's thyroid is aggravated by the administration of 100 I.U. of TSH, as shown by the heavy intrafollicular infiltration It seems also that this hormone lessens the degree of structural change in the follicular cells Cortisone, administered in doses of 5 mg every 2 days to rats subjected to thyroid auto-immunization, reduced fibroblast and lymph-cell reactions These studies show that hypertrophic and hyperplastic thyroid tissue obtained by an iodine-deficient diet or methylthiouracil is also antigenic, and that the immunity response of the thyroid is modified by TSH and cortisone [41]

This research as a whole does not allow any definitive conclusions to be drawn about the role of pathological conditions due to immunity reactions, either in the initial development of goitre or, more especially, in the subsequent changes in the structure of the goitre. However, it furnishes arguments in support of the possible role of this process in the gradual change from the lesions of hyperplastic parenchymatous goitre to those of colloid goitre and the late sclerotic and nodular form

The intervention of immunopathological factors might explain the transition from the deficiency type of lesion to the atrophic degenerative type.

Studies of the follicular cell with the electron microscope, though still at a very early stage, reveal structural changes in the mitochondria, the Golgi apparatus, and the cytoplasm network. The thyroid cell, lacking iodinated hormones, suffers in its metabolism, and this situation is aggravated by continual stimulation by TSH, which tries to act upon a cell unable to provide a secretory response

Death of the cell, accompanied by permeability of the follicular membrane, allows immunity reactions to occur and leads to a stage of irreversible degenerative lesions At this stage, the thyroid cell no longer takes up iodine and correction of the iodine deficiency no longer cures the condition, as is well known from attempts to treat old goitres. In the development of experimental goitre, the older the goitrogenic process the more frequently this occurs and the more pronounced are the degenerative changes

We are inclined to the view that the change from the lesions of iodine-deficiency goitre to those of degeneration, with atrophy and cytolysis, is accompanied by the formation of antigens that subsequently cause the interstitial lesions of old, scleronodular goitres. It follows from this that, from the moment thyroid antibodies appear in the blood or tissues of an individual with goitre, the process of goitre formation is self-maintained by immunity reactions and is irreversible to an extent that depends on the character and date of appearance of the lesions.

Discussion

Taken as a whole, this research work confirms that iodine deficiency is the *sine qua non* of experimental goitre, and its significance must not be overlooked in any attempt to discover the other factors involved in the production of goitre in endemic zones.[9, 37, 39, 40, 43]

There is also the concept of endogenous defect of the thyroid, characterized by the fact that iodine ingested in adequate amounts does not reach the thyroid or is not made use of in hormone synthesis The endogenous causes of this phenomenon are manifold Among them our studies have shown the role of the nervous system, of certain hormones, and of thyroid immunopathology We have tried to elucidate the mechanism whereby these factors slow down, speed up, or otherwise help in the development of the hypertrophic, hyperplastic process of goitre formation set off by iodine deficiency.

Starting from the principle that any factor hindering iodine metabolism, and in particular its utilization by the thyroid, is potentially goitrogenic, we have shown that excitation of the CNS either directly or through drugs accelerates the process of formation of a goitre induced by methylthiouracil or a diet rich in cabbage. Inhibition of the CNS slows the process, as was confirmed by a reduced uptake of ^{131}I, a fall in the amount of TSH and iodinated hormones, and weight and structural changes in the thyroid. We have also found that resection of the sympathetic and parasympathetic nerves of the thyroid in rabbits decreases hyperplasia and hypertrophy due to methylthiouracil, reduces iodine uptake, increases the amount of colloid, and produces a *microfollicular, colloido-parenchymatous goitre* These changes appear not only in the denervated lobe but also in the intact lobe, which demonstrates their reflex character.

Chromophilic changes in the pituitary associated with goitre induced by methylthiouracil also argue in favour of the hypothesis that sympathectomy acts at a distance as well as locally.

Studies on the role of the network of nerves within the gland demonstrated that Novocaine or rubber injected into the thyroid can prevent iodine from being taken up, and lower the level of PBI and the amount of

TSH and thyroid hormone. In these experiments we observed inhibition of TSH secretion and a secondary fall in thyroid response. We also noted the fall in acetylcholine in the thyroid after injection of Novocaine. Inhibition of TSH after injection of rubber into the thyroid was shown by the small amount of compensatory hypertrophy after unilateral lobectomy.

That the pituitary and the adrenals play a part in the hormone imbalance produced by iodine deficiency of exogenous origin was shown by the hypertrophy of these glands that accompanied the appearance of goitre in ducks reared in an endemic area. Certain hormones were able to modify the intensity and quality of the process of goitre formation due to iodine deficiency in the diet. Cortisone, desoxycorticosterone, oestradiol, testosterone and corticosterone speeded up the transformation of iodine-deficient parenchymatous goitre into microfollicular colloid goitre. The steroid hormones and the protein hormones—the growth hormone and pineal and thymus extracts—reduced the weight of iodine-deficiency goitre by 50%-65%. The action of these hormones probably varies with the dose injected, small doses stimulating and large doses inhibiting, as was shown by changes in the uptake of ^{131}I and in thyroid structure under the influence of oestradiol.

In animals kept for 3 months on an iodine-deficient diet that had led to the appearance of a goitre, we observed that thyroid response to an external stimulus—an injection of TSH—was reduced or weakened, showing the decrease in thyroid uptake of ^{131}I. Since structural changes appear during the various stages in the development of iodine-deficiency goitre —parenchymatous hyperplasia, colloid goitre and degenerated goitre— and since in these circumstances there is hypersecretion of TSH, we hold the view that variations must exist in the response of goitrogenous tissue to TSH during this process.

Accepting the hypothesis that thyroid tissue damaged by the goitrogenic process is antigenic, and that the antibodies formed as a result can play a part in the continuation of the process, we studied auto- and iso-immunization in the normal thyroid and in goitre. Three months after administering a suspension of iso-antigen to rabbits, we succeeded in inducing a microfollicular parenchymatous goitre. Our experiments also showed that iodine-deficiency goitres have very little antigenicity, and that antigenitity can be maintained in methylthiouracil-induced goitres, circulating antibodies then appearing that are not found in iodine-deficient goitres. We also demonstrated that cortisone and TSH can reduce the cellular and fibroblastic reaction of the thyroid to auto- and iso-immunization.

These studies prove that TSH may have an unfavourable effect on the development of immunity goitres, and provide justification for the therapeutic use of cortisone. The histological picture revealed in the course of the experiments leads us to believe that the appearance of circulating antibodies in a person suffering from a goitre indicates that the process of goitre

formation (deficiency, then degeneration and cytolysis) has been left behind, and that a process of auto-aggression within the thyroid tissue has begun, with all its consequences.

Taken as a whole, the findings in these experiments on goitre show the complexity of the mechanism whereby the goitrogenic process is initiated and develops. In this process iodine deficiency and pituitary and thyroid reactions thereto are the fundamental, but not the only elements.

REFERENCES

1 Amiragova, M G (1958) *Le mecanisme régulateur des fonctions de la glande thyroïde par le cortex cérébral.* In *Proceedings of the Second United Nations International Conference on the Peaceful Uses of Atomic Energy*, Geneva, vol 10, p 82

2 Angelescu, E et al (1958) *Modificările presiunii arteriale si a respirației la câine, după infiltrația de novocaină intratiroidiană* In Gușa endemică, 2, 321

3. Astwood, E et al (1943) *Endocrinology*, 32, 210

4 Bikov, K. M (1952) *Scoarța cerebrală și organele interne*, București, Editura de Stat

5 Cassano, C, Baschieri, L & Andreani, D (1957) *Rass Fisiopat clin ter*, 29, 253

6 Chesney, A M, Clawson, T A & Webster, B (1928) *Bull Johns Hopk. Hosp*, 43, 261

7 Costa, A, Cottino, F & Ferrario, G. (1953) *Ann Endocr (Paris)*, 14, 995

8 Danielopolu, D (1936) *Les thyroïdies*, Paris, Masson

9 De Courcy, J & De Courcy, C B (1951) *Trans Amer Goiter Ass*, 4, 3

10 *Doniach, D & Roitt, M J (1957) J clin Endocr*, 17, 1293

11 Fertman, M B & Curtis, G. M (1951) *J clin Endocr*, 11, 1361

12 Gear, J (1955) *Acta med scand*, 152, Suppl No 306, p 39

13 Greer, M A & Astwood, E (1948) *Endocrinology*, 43, 105

14 Kabak, J M (1950) *Stud Cercet Endocr*, 1, 13

15 Levine, H., Remington, R E. & von Kolnitz, H (1933) *J Nutr*, 6, 325

16 Lupulescu, A, Negoescu, I, Niculescu-Zinca, D & Cocu, F. (1960) *Stud Cercet Endocr*, No 3 (in press)

17 Mackenzie, J B et al (1941) *Science*, 94, 518

18 Medvedeeva, N. B (1946) *Experimentalnaia endokrinologhii*, Moscow, Medghiz

19. Milcu, S M & Vrabiescu, A (1958) *Contribuții la studiul interorecepției tiroidiene Acțiunea hipotiroidizantă a blocajului novocainic tiroidian. Comunicație la Conferința de Terapie reflectorie și interorecepție din Riga, USSR, 1958*

20 Milcu, S M & Vrabiescu, A (1960) *Stud Cercet Endocr*, 11, No 4 (in press)

21. *Milcu, S M, Belloiu, D & Negoescu, I (1957) Distribuția distrofiei endemice tireopate pe valea râului Argeș* In *Gușa endemică*, 1, 175

22 [illegible] ...ndiol ... lings ... ork, vol. 10, p. 376

23 Milcu, S M, Negoescu, I & Lupulescu, A (1957) *Acțiunea sistemului nervos central asupra gușii experimentale produsă prin alimentația cu varză* In· *Gușa endemică*, 1, 217

24 Milcu, S. M, Simionescu, N. & Maxim-Bercea, I. (1955) *Buletin stiint. Secția st. med a Acad. R P.R*, 7, No 2, 499

25 Milcu, S M, Vrabiescu, A & Antonescu, M (1958) *Comunicarile Academiei R P R.*, 8, 99

26 Milcu, S M, Vrabiescu, A & Maxim-Bercea, I (1956) *Stud Cercet Endocr*, 7, 3
27. Milcu, S M, Belloiu, D, & Holban, R & Sahleanu, V (1952) *Stud Cercet Endocr*, 3, 347
28 Milcu, S M, Potop, I, Vrabiescu, A & Felix, E (1960) *Rev Sci méd (București)*, (in press)
29 Milcu, S M, Simionescu, N, Bojinescu, A. & Hirson, M. (1957) *Fixarea si utilizarea radioiodului (I_{131}) de către tiroida denervată* In *Guşa endemică*, 1, 257
30 Milcu, S M, Vrabiescu, A, Maxim-Bercea, I & Macrineanu, A (1960) *Comunicările Academiei R P R*, 5 (in press)
31 Milcu, S M, Vrabiescu, A, Zimmel, H & Maxim-Bercea, I (1959) *Stud. Cercet Endocr*, No 3, 293
32 Milcu, S M, Belloiu, D, Holban, R Sahleanu, V & Negoescu, I (1957) *Influenţa decorticării si a zguduirilor nervoase asupra acţiunii tiroxinei si antitiroidienelor de sinteză* In *Guşa endemică*, 1, 291
33 Milcu, S M, Lupulescu, A, Negoescu, I, Bojinescu, A & Cocu, F (1956) *Rev Sci méd (București)*, 1, 47
34 Milcu, S M, Negoescu, I, Petrescu, C, Lupulescu, A & Cocu, F (1957) *Contribuţii la acţiunea clorpromazinei asupra glandei tiroide* In *Guşa endemică*, 1, 235
35 Milcu, S M, Pop, A, Lupulescu, A, Heitmanek, C & Simionescu, L (1960) *Rev Sci méd (București)*, 1 (in press)
36 Monney, W, Rall, Y & Rawson, R (1952) *J clin Endocr*, 12, 1495
37 Nicolaev, O V (1952) *Endemiceskii zob*, Moscow, Medghiz
38 Niculescu, T I et al (1952) *Comunicarile Acad R P R*, 2, 383
39 Parhon, C I & Goldstein, M (1930) *Traite d'Endocrinologie*, Jassy
40 Pitt-Rivers, R, Tata, J R & Trotter, W R (1959) *The thyroid hormones*, London, Pergamon Press
41 Pop, A, Lupulescu, A, Heitmanek, C & Simionescu, L (1960) *Stud Cercet Endocr*, 1, 33
42 Rose, N R & Witebsky, E (1956) *J Immunol*, 76, 417
43 Stanbury, J B et al (1954) *Endemic goiter*, Cambridge, Harvard University Press
44 Sterescu, N & Zimmel, H (1958) *Stud Cercet Fiziol*, 9, 323
45 Voitkevici, A (1953) *Usp sovrem biologhii*, No 1
46 Vrabiescu, A (1960) *Rev Sci med* (in press)
47 Vrabiescu, A, Zimmel, H & Maxim-Bercea, I (1959) *Stud Cercet Endocr*, 10, 293
48 Witebsky, E & Rose, N R (1956) *J Immunol*, 76, 408
49 Witebsky, E, Rose, N R, Terplan, K & Egan, R (1957) *J Amer med Ass*, 165, 1439



PATHOLOGICAL ANATOMY OF ENDEMIC GOITRE

Dr M. P DE SMET *

The Normal Thyroid Gland

Anatomy, histology and cytology of the normal thyroid gland

The thyroid is the largest endocrine gland in the adult, in children, only the thymus is larger In adults, the normal thyroid gland in areas free from goitre weighs about 20 g The dimensions of each lobe vary around 4-7 cm in length, 2 5 cm in width, and 1 75 cm in depth The isthmus which connects the two lobes is square in shape, 2 cm² in area, and from 0 2 to 0 6 cm in depth Cases of hemi-aplasia of the gland have been described [96] According to Hull,[47] the isthmus may be absent in 3 6% of thyroid glands, but other authors, such as Anderson,[1] consider this anomaly to be less common

The gland is invested by a fibrous capsule from which septa proceed into the parenchyma, dividing it into fairly regular lobules In reactional hypertrophy these lobules acquire some degree of autonomy, and may develop independently of one another [118] According to Johnson,[52] the lobules consist of about 20-40 secretory units, termed follicles (vesicles, acini, or alveoli). Each lobule has its own arteriole

Kin[illegible]
a sticky [illegible]
the co[illegible]
0 3 mm,[105, 139] or of 0 163 mm after maceration with hydrochloric acid [49] Jackson observed more oval follicles in young subjects than in adults [49] The autoradiographic studies made by Taylor [119] perhaps explain this difference in diameter On examining slightly hypertrophied glands, obtained by subtotal thyroidectomy, he found that the diameter of active follicles was, on the average, only half or one-third of the diameter of non-

* Médecin Directeur de l'Institut National pour l'Etude Agronomique au Congo belge, Yangambi, Belgian Congo, and Member of the Academie royale belge des Sciences d'Outre-Mer

active follicles. Williams,[135] by means of a technique involving transillumination of thyroid tissue transplanted into a rabbit's ear, was also able to show temporary inactivity in several follicles, with increase in diameter and partial follicular collapse after secretory activity.

The follicles are surrounded by loose connective tissue containing vessels and nerves. Each secretory unit is provided with an arteriole that ends in a capillary network surrounding the follicle. Sunder-Plassmann [115] observed neurohormonal cells in the follicle and considered them to be under vagus influence, mediated by a terminal network; however, Ludwig [61] was unable to confirm the existence of these cells in experiments on several species of laboratory animal Nonidez,[88] in his important work on the innervation of the thyroid follicle and the follicular cell, concluded that neural influence was mediated through the blood vessels A special study of these vessels was made by Modell,[78] who demonstrated the existence of arteriovenous anastomoses, making possible capillary control of the uptake of the hormone.

Four arteries carry the adult's five litres of blood through the thyroid every hour. After the lungs and the kidneys, the thyroid is one of the organs that receives most blood. 4 ml per minute per gram of tissue. These figures explain the tendency to haemorrhage in this organ—all the greater, as Major [61] has shown, because the arteries do not penetrate into the parenchyma but divide immediately at the surface of the gland into a network of arterioles

The epithelium in the normal thyroid follicle is regular, cubical, and 15 microns thick [100] With increased activity, the cells lengthen; in inactivity, their length decreases These cells are oriented in the same direction and secrete a colloid substance into the lumen of the follicle The colloid is highly eosinophilic in the adult, but becomes basophilic in old people from an increase in nucleoproteins The colloid is digested by various enzymes, including certain amylases.[58]

It has been found that certain intracellular elements are related to cellular activity. When the gland is hyperactive, the mitochondria hypertrophy [15, 34, 108, 109] Cramer and Ludford [16] have interpreted this increase in the size of the mitochondria as indicating an increase in the intracellular surface area, leading to a decrease in surface tension and consequently accumulation of cytoplasm lipids and increase in the permeability of the cell membrane

The Golgi apparatus, another cytoplasmic structure, also becomes hypertrophied in glandular hyperactivity, lipoid droplets accumulating and the network increasing in size.[16] Porter, Claude & Fullam [98] were able to confirm the existence of these lipoid bodies by electron microscopy.

Using the Caspersson technique, Koch [56] measured the volume of the nuclei in the rat; after injection of a thyrotropic hormone he found a rapid increase in mean volume from 98 to 150 cubic microns This increase in nuclear volume is a good test for follicular activity

Growth of the normal thyroid gland

The follicles appear when the embryo is 24 mm long.[85] They take the form of groups of cells arranged concentrically in the plates forming the germinal bud of the gland.

When the embryo is 5 cm long the follicles develop a lumen, and at 6 cm colloid appears. At 16 cm the formation of new follicles stops and only the size of the gland continues to increase. According to Marine,[68] production of new follicles continues in the embryo under pathological conditions.

At birth, there are three possible types of structure: the solid type, the type with a lumen, either well developed or collapsed, and the mixed type.[27]

In 1938, Rice published an important study on the morphological development of the thyroid from birth to the age of 80.[103] At birth, the follicles have a cubical epithelium, are round, and are smaller than in adults. The stroma contains a few epithelial cells between the acini, whereas in the adult it has none. Except on the periphery of the lobules, which are demarcated by fibrous bands, the stroma is loose. Rice noted the presence of parenchymatous nodules, in particular after puberty, and also in clinically normal thyroids.

With advancing age, the normal histological structure undergoes changes. Clerc,[12] Vogeler,[126] Lowe,[59] Doglioti & Nuzzi-Nutti,[25] Garau,[32] Nolan,[83] Rice[103] and Andrews[2] studied the changes occurring in old age. They found a more fibrous stroma, more basophilic colloid, epithelium desquamating into the enlarging follicles, and an increased number of interacinar epithelial cells.[33] Doglioti & Nuzzi-Nutti[25] observed an increased number of granules in the acinar cells which they attributed to regeneration with junctional reactivation in old age.

Weight and volume of the normal thyroid gland

The average weight of the gland depends on the subject's weight, sex, and place of origin, on various physiological states (puberty, pregnancy, menopause), and on pathological changes (nodules, inflammatory conditions, tumours), the latter being more often seen in regions of endemic goitre.

In 1910, Kloeppel[53] found the thyroid in Central Europe to weigh 5 g in the newborn baby, 34-41 g in the adult, and 30-32 g in persons of 51 to 65 years. At the present day, with the general improvement in nutrition, prophylaxis with iodized salt, and the import of food from non-endemic areas, these figures are considered to indicate a pathological state. In 1924 Wegelin[130] in Berne had accepted 3 g as the normal weight at birth. However, several glands exceeding 3 g in weight were found to show a hyperaemia which disappeared after 2-3 days, so that the weight again became normal after this period of time. At present, Thalmann[122] regards as normal a weight of 1-1.25 g per kilogram of body-weight in newborn babies in Switzerland.

The change in the weight of the normal gland in a non-goitrous region was recently studied by the author in 140 autopsies in the Belgian Congo. The average weight of adults was 55 kg in the area under study; and the average weight of the thyroid gland was as follows·

Birth	2 g
1 year	2 g
2 years	3 g
5 years	4 g
Prepubertal years	10 g
15-20	18 g
20-50	20-25 g
50-70	15-20 g

The thyroid is probably heavier in temperate countries, where the average weight of adults is about 70 kg Marine [65] calculated the weight of the thyroid gland in relation to body-weight, and found that the ratio does not exceed 0.35 g of gland per kg of body-weight. On the average, then, a man of 70 kg would have a thyroid weighing 24 5 g However, in Iceland Sigurjonsson [110, 111] found that the average weight of the gland was 14 g in adult men and 11 6 g in women But glands there are richer in iodine, and though small contain as much iodine as the much heavier glands studied by Marine.

McCarrison [74] studied the weight of the thyroid in relation to body-weight in animals He showed that in the non-goitrous animal there is a constant ratio at different ages between the weight of the thyroid and body-weight This ratio does not apply to the goitrous animal because of the accumulation of colloid in the gland There is a special ratio between the weigth of the thyorid gland and body-weight at puberty. This "physiological goitre ", also observed in non-endemic regions, is only a temporary and reversible parenchymatous hypertrophy, and is not a manifestation of endemic goitre. Moreover, in non-endemic regions, nodules do not usually occur in this variety of goitre

In endemic regions the weight of the gland before and during puberty is disproportionately high in relation to body-weight, during this period sex has a marked influence Olesen & Taylor [92, 93] found that the size of the gland in boys, although smaller than in girls, increases before puberty and begins to decrease after, whereas in girls it continues to increase after puberty and only decreases during adolescence

In 1924, Aschoff [4] gave the classical description of the six stages in the development of the thyroid.

(1) increase in size at birth,

(2) decrease in early childhood;

(3) increase before and during puberty;

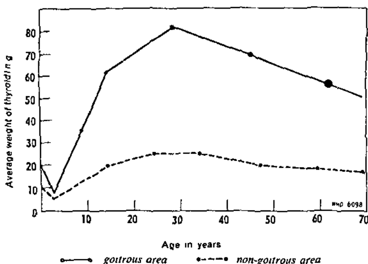
(4) decrease after puberty (adolescence);

(5) normal during adult life;

(6) atrophy in old age with possible regeneration of thyroid function

The growth curve of the goitrous thyroid gland shows many analogies with that of the non-goitrous one (Fig 1) It shows that the weight in goitrous regions is distinctly greater and that variations with age are much more pronounced

FIG 1 AVERAGE WEIGHT OF THE THYROID GLAND IN GOITROUS AND NON-GOITROUS AREAS



Reproduced, by permission, from Aschoff[4]

The gland is normally stable in weight after adolescence The weight of normal thyroid glands has been studied by various authors [50, 75, 81, 90, 101] Mortensen's two graphs compare the average weights of normal thyroid glands in males and females (Fig 2), the differences are insignificant

Hull[47] studied the weight of the thyroid in adults in Colorado, USA He found, in a series of glands obtained by autopsy from adults in this potentially endemic region, an average weight of 32 4 g in men and 24 7 g in women, the weight of the glands without nodules was, respectively, 19 g and 17 7 g In his series he found, respectively, 62 2% and 67% of glands with nodules Taking as his criterion of goitre a thyroid weight of more than 35 g, as suggested by Arndt[3], Hull found 21 3% of glands to have goitrous hypertrophy

Senility leads to a decrease in the weight of the gland It is at this age in particular that nodules are found and, for this reason, the variation in weight in old age is pronounced.

The change in the weight of the normal gland in a non-goitrous region was recently studied by the author in 140 autopsies in the Belgian Congo. The average weight of adults was 55 kg in the area under study; and the average weight of the thyroid gland was as follows:

Birth	2 g
1 year	2 g
2 years	3 g
5 years	4 g
Prepubertal years	10 g
15-20	18 g
20-50	20-25 g
50-70	15-20 g

The thyroid is probably heavier in temperate countries, where the average weight of adults is about 70 kg. Marine[65] calculated the weight of the thyroid gland in relation to body-weight, and found that the ratio does not exceed 0.35 g of gland per kg of body-weight. On the average, then, a man of 70 kg would have a thyroid weighing 24.5 g. However, in Iceland Sigurjonsson[110, 111] found that the average weight of the gland was 14 g in adult men and 11 6 g in women But glands there are richer in iodine, and though small contain as much iodine as the much heavier glands studied by Marine.

McCarrison[71] studied the weight of the thyroid in relation to body-weight in animals He showed that in the non-goitrous animal there is a constant ratio at different ages between the weight of the thyroid and body-weight This ratio does not apply to the goitrous animal because of the accumulation of colloid in the gland There is a special ratio between the weigth of the thyorid gland and body-weight at puberty. This "physiological goitre", also observed in non-endemic regions, is only a temporary and reversible parenchymatous hypertrophy, and is not a manifestation of endemic goitre Moreover, in non-endemic regions, nodules do not usually occur in this variety of goitre

In endemic regions the weight of the gland before and during puberty is disproportionately high in relation to body-weight; during this period sex has a marked influence. Olesen & Taylor[92, 93] found that the size of the gland in boys, although smaller than in girls, increases before puberty and begins to decrease after, whereas in girls it continues to increase after puberty and only decreases during adolescence

In 1924, Aschoff[4] gave the classical description of the six stages in the development of the thyroid.

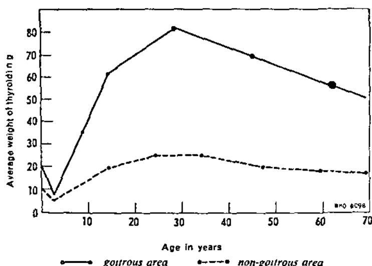
(1) increase in size at birth,
(2) decrease in early childhood,
(3) increase before and during puberty;
(4) decrease after puberty (adolescence);

(5) normal during adult life;

(6) atrophy in old age with possible regeneration of thyroid function.

The growth curve of the goitrous thyroid gland shows many analogies with that of the non-goitrous one (Fig. 1) It shows that the weight in goitrous regions is distinctly greater and that variations with age are much more pronounced

FIG 1. AVERAGE WEIGHT OF THE THYROID GLAND IN GOITROUS AND NON-GOITROUS AREAS



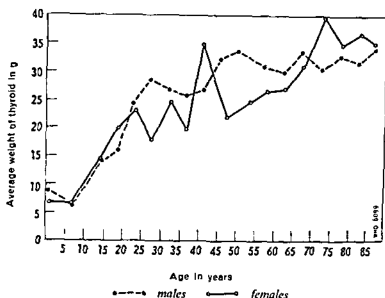
Reproduced by permission, from Aschoff[4]

The gland is normally stable in weight after adolescence The weight of normal thyroid glands has been studied by various authors.[50, 75, 81, 90, 101] Mortensen's two graphs compare the average weights of normal thyroid glands in males and females (Fig. 2); the differences are insignificant.

Hull[47] studied the weight of the thyroid in adults in Colorado, USA He found, in a series of glands obtained by autopsy from adults in this potentially endemic region, an average weight of 32 4 g in men and 24 7 g in women; the weight of the glands without nodules was, respectively, 19 g and 17 7 g In his series he found, respectively, 62 2% and 67% of glands with nodules Taking as his criterion of goitre a thyroid weight of more than 35 g, as suggested by Arndt[3], Hull found 21 3% of glands to have goitrous hypertrophy.

Senility leads to a decrease in the weight of the gland. It is at this age in particular that nodules are found and, for this reason, the variation in weight in old age is pronounced

FIG. 2. RELATIONSHIP OF AGE AND SEX TO WEIGHT OF THE THYROID GLAND



Reproduced, by permission, from Mortensen, Woolner & Bennett [1]

Origin and Definition of Endemic Goitre

This review of the structure and weight of the normal thyroid gland will facilitate understanding of pathological changes and enable goitre to be defined by a *physical examination taking into account the structure* and weight of the gland

A geographical region is said to be endemic if more than 10% of the population show clinical signs of generalized or localized thyroid hypertrophy Areas of endemic goitre are usually characterized by a lack of iodine in the soil, resulting in a drinking-water of very low iodine concentration. In such regions goitre may be regarded as the way in which the thyroid gland adapts itself to a deficiency state. This adaptation may also occur as a result of factors that interfere with the metabolic utilization or the absorption of iodine from food.[101] Goitres caused by excessive loss of iodine in the urine are rare, and not endemic in nature [8]

The origin of endemic goitre thus seems to lie outside the thyroid gland Iodine deficiency leads to anatomical changes in the gland. These changes take time to become organized, but thereafter may pursue their own independent development [36]

Clinically, endemic goitre appears as a general or local *hypertrophy* of the thyroid parenchyma. Perez, Scrimshaw & Muñoz [95] do not admit the

existence of a goitre unless the thyroid has become 4-5 times its normal size and is visible; moreover, only glands containing palpable but not necessarily visible nodules are counted as endemic goitres

In Africa, Pales [94] considers all palpable thyroids to be goitres. In the adult Bantu any palpable thyroid weighs 35 g or more From the viewpoint of weight, Arndt [3] and Hazard & Kaufman [39] regard any thyroid weighing more than 35 g as goitrous In Africa, Pales' criterion is thus entirely applicable It may be extended to include countries with a temperate climate, and even those with a cold climate (Iceland, or the countries inhabited by Eskimos)

Thyroid hypertrophy may take the form solely of nodules in a gland of normal weight or even in an atrophied gland This, again, must be regarded as endemic goitre, especially from the viewpoint of structure. In reality, as Hull [47] showed, the majority of glands containing nodules weigh more than 35 g and are therefore already goitres in which nodules are only a secondary manifestation

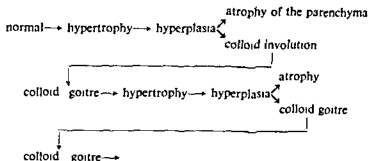
To be clinically detectable, nodules must have a diameter of at least 10 mm, since below this they are no longer palpable. Schlesinger, Gargill & Saxe [107] found that 8 2% of nodules had a diameter of at least 10 mm in Massachusetts, a non-endemic region of the United States On the other hand, in a potentially endemic region Mortensen [71] found 21% of nodules in the excised gland palpable (about 10 mm in diameter) These two series are of clinically normal thyroids, i e, non-hypertrophic ones, examined at autopsy in patients who had shown no thyroid symptoms at any time during their lives

The endemic region is thus characterized either by the presence of glands that are normal in weight but contain nodules in more than 10% of cases, or by goitres with or without nodules, or by atrophied glands with nodules in some cases of chronic malnutrition. As regards this last form, Tejada [121] reported in Guatemala fibrous atrophy of the gland, accompanied by nodules, and in association with malnutrition, in these cases, another criterion of endemicity, in addition to the weight and size of the gland, is the presence of palpable or visible nodules.

By definition, endemic goitre is thus glandular hypertrophy observed in a region recognized as endemic The thyroid is palpable (weighing more than 35 g) and often contains nodules These nodules, particularly when multiple, are an index of the length of time during which the endemic state has been in existence, and of its seriousness

Goitrogenesis

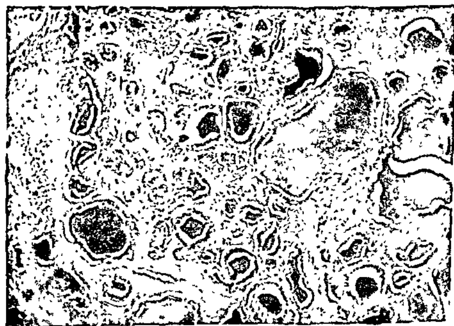
Marine's classic theory of goitrogenesis [66] distinguishes an epithelial hyperplastic phase and one of involution If these processes are repeated, the size of the gland continues to increase until a goitre develops.



The hyperplastic (parenchymatous) phase of endemic goitre

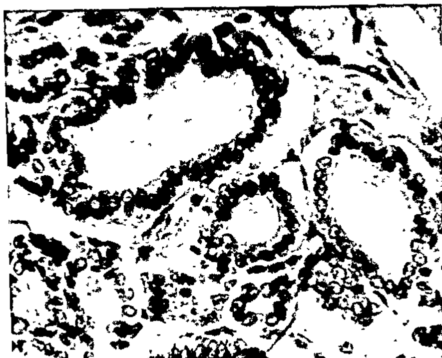
This phase is temporary, but nevertheless has a pathological reality. Hyperplasia may be either localized or generalized. In contrast to exophthalmic goitre, in which the histological picture is similar, the epithelium does not show eosinophilic degeneration, the stroma shows no lymphoid reaction, and lobulation is well preserved Two kinds of follicles can be seen. microfollicles (Fig. 3) and macrofollicles with a folded wall showing evaginations (papillae or buds termed "Sanderson polsters") giving this form the appearance of vegetation (Fig 4). The epithelium is cubical

FIG. 3. GOITROUS THYROID SHOWING ADJACENT AREAS OF MICROFOLLICULAR AND MACROFOLLICULAR HYPERPLASIA



×100

FIG. 4. THYROID HYPERPLASIA SHOWING EVAGINATIONS OF THE FOLLICULAR WALLS

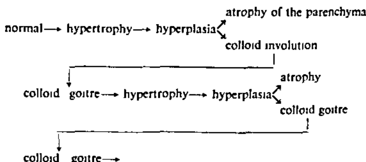


×6400 Reproduced by courtesy of Dr C Tejada, Guatemala

or columnar and the nuclei are regular and similar to each other, but there is no mitosis [97] (Fig 5) The colloid is gradually reabsorbed: first vacuoles appear, then the colloid vanishes, here and there an occasional follicle can still be seen full of eosinophilic colloid

Glandular hypertrophy is diffuse, of recent date, and vascular, and on section has the appearance of parenchymatous goitre This picture, also found in nodules, is termed microfollicular adenoma, but there the regular lobulation characteristic of the normal thyroid is no longer seen (cf Fig 11, page 334) The pseudopapillary macrofollicular form indicates a reactional phase that begins when the tendency to follicular dilatation appears as a result of thyroid decompensation

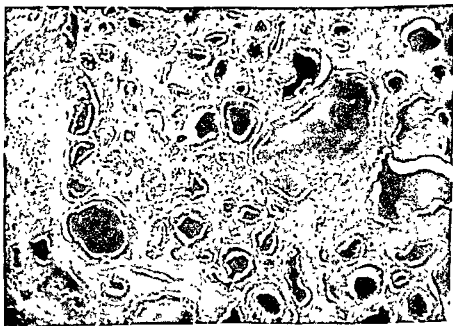
According to Marine,[67] these hyperplastic changes occur only if the iodine content of the gland is below 1% of its dry weight In these circumstances, the production of thyroid hormone is inadequate. Lack of thyroxine may be absolute, because of iodine deficiency or because anti-thyroid substances hinder the uptake of iodine by the follicle, or relative, because of an exaggerated peripheral demand, or virtual, because of pituitary stimulation [36] and it is the cause of excessive production of thyrotropic



The hyperplastic (parenchymatous) phase of endemic goitre

This phase is temporary, but nevertheless has a pathological reality. Hyperplasia may be either localized or generalized. In contrast to exophthalmic goitre, in which the histological picture is similar, the epithelium does not show eosinophilic degeneration, the stroma shows no lymphoid reaction, and lobulation is well preserved. Two kinds of follicles can be seen: microfollicles (Fig. 3) and macrofollicles with a folded wall showing evaginations (papillae or buds termed "Sanderson polsters") giving this form the appearance of vegetation (Fig. 4) The epithelium is cubical

FIG 3 GOITROUS THYROID SHOWING ADJACENT AREAS OF MICROFOLLICULAR AND MACROFOLLICULAR HYPERPLASIA



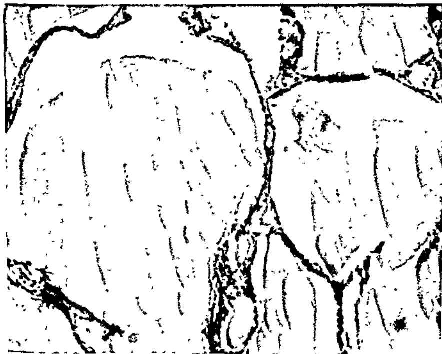
×100

will not take part in secretion and will consequently undergo structural involution.

Thus the succession of hyperplastic phases in the gland involves structural changes because of the formation of inactive areas which are at first in a resting state and subsequently undergo hypoplastic involution In endemic regions these successive hyperplastic phases develop under the stimulus of iodine deficiency

Involution is shown by a decrease in the volume of the nucleus, then of *the cell The mitochondria disappear from the cytoplasm, the epithelium* becomes definitively flattened, and follicles, no longer active, fill up with colloid which they are unable to metabolize (Fig 6) Their diameter increases from 300 to 900 and even to 1500 microns [139]

FIG 6. INVOLUTIONAL PHASE OF MACROFOLLICULAR GOITRE



×2000

Reproduced by courtesy of Dr C Tejada, Guatemala

Apart from this epithelial component, there is a rich stroma in endemic goitre, consisting of loose fibrous or hyaline connective tissue. The circulatory changes—the most frequent of which are hyperaemia, intraparenchymatous haemorrhage, and then oedema (Table II, page 336)—are less characteristic than in nodular goitre.

FIG. 5. PAPILLARY HYPERPLASIA OF THE THYROID



×350

hormone and consequently of a hypertrophic reaction, followed by hyperplasia of the follicular epithelium

Resting phase and phase of involution

The hyperplastic reaction cannot continue indefinitely. When it does not succeed in taking up the iodine required for maintenance of the endocrine balance, it comes to a stop, and atrophy of the parenchyma ensues. In glandular atrophy, there can clearly be no question of goitre, but this is a rare phemonenon

A more frequent development in non-goitrogenic areas is the return to normal of the histological picture as a result of the gradual reappearance of colloid in the follicles, which enlarge and resume their normal diameter of 300 microns The hyperplastic epithelium returns to its cubical shape, about 15 microns thick. The gland may even enter a resting phase, following an increase in the intake of iodine The epithelium becomes flattened as the follicle fills with colloid This is the normal picture of the thyroid in Iceland, where there seems to be an abundant iodine intake.[111]

In endemic areas, however, if a fresh iodine shortage occurs, hyperplasia will usually develop subsequently in certain parts of the gland. These centres of activity will continue to maintain a satisfactory thyroid balance in the subject. Neighbouring areas, consisting of resting follicles,

ingly frequent from the age of puberty onwards. In a more recent study Mortensen, Woolner & Bennett [81] studied 821 glands from persons in whom neither history nor clinical examination had revealed trouble with the thyroid. Fine 2-mm sections of the glands in this series showed nodules to be present macroscopically in 49 5% of cases (12.2% uninodular and 37.3% multinodular) and to develop mainly after puberty.

Wölfler [141, 142] had advanced the theory that these benign tumours arise from embryonic epithelial rests Aschoff [4] also thought that nodules have nothing to do with the problem of endemic goitre, but are indicative of a benign neoplasia, having no connexion with hyperplasia and involution since they differ in structure from the surrounding thyroid tissues and since senile atrophy does not occur in them at the same time as it does in the internodular parenchyma

Taking an opposite point of view, Wegelin [130, 131, 134] argued in favour of a close relationship between these nodules and goitre This view was supported by Rienhoff for the regressive nodule, and by Rice,[103] Rawson,[99] and McGavack [76] for the hyperplastic nodule

These two schools are still in opposition. The truth is that the problem of the pathogenesis of the thyroid nodule, even in non-endemic regions, is very complex and is still not understood According to Stanbury,[113] goitre is a constitutional disease in non-endemic regions, appearing for the first time as adolescent goitre and developing in about 25% of cases into toxic goitre

It has been observed that endemic and, above all, hyperendemic regions are characterized by the early appearance of parenchymatous and colloid nodules before puberty However, progression to toxic goitre has only rarely been observed among the Bantu by Higginson [45] or by the present author [20]

In pre-pubertal children in the large endemic area of the Ueles (North Congo) I have found nodular formations in some 10% of those with glandular hypertrophy This hypertrophy occurs on the average in 80% of children aged 5-10 In this connexion we may mention Kimball's [53] hypothesis that there is a relationship between pre-pubertal nodules and severe iodine deficiency during pregnancy—a relationship observed solely in hyperendemic areas, apart from a few exceptional cases in low endemic areas The following example shows that this hypothesis is probably correct

A subtotal thyroidectomy had been performed on a woman with a large fourth-degree colloid goitre, and, as often happens in the less developed countries, the patient did not come back to the clinic for post-operative care She became pregnant shortly after having been operated upon and returned to the hospital nine months later: caesarean section was necessary to deliver the large baby, which weighed 4300 grams (the mother herself weighed only 45 kg) The child, which was born with a nodular hyperplastic goitre, died Its thyroid gland weighed 7 5 g, had a nodular surface, and was

To sum up, the diffuse form of endemic goitre in the adult is more frequently colloid (atrophic) than *parenchymatous* (hyperplastic) The structure of the diffuse colloid form is of a distinctly follicular type, with preponderance of the macrofollicular component in an abundant loose fibrous connective tissue *Regressive changes in the stroma are, like the* circulatory upsets, of little significance.

According to Frattini et al.[31] histochemical tests indicate lowered metabolic activity, histoautoradiography and *radiochromatography* reveal the existence of an intense iodine uptake—particularly by the microfollicular areas—and full but lowered secretory activity, with preponderance of the simpler aminoacids (Table II)

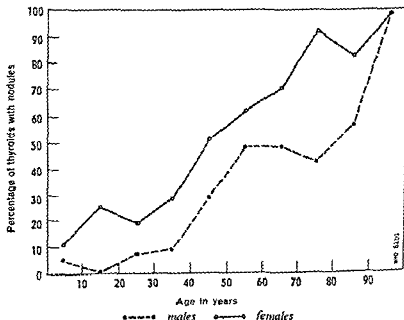
The Thyroid Nodule

Pathogenesis

In the cycle as suggested by Marine,[88] the hyperplastic reaction, at first general, may subsequently become local It takes place in the nodule, this being any macroscopic tumour that can be distinguished from homogeneous thyroid tissue.

During the life of the gland, nodules seem gradually to become more common (Fig 7) Aschoff[4] and Rice[103] found that nodules were increas-

FIG 7 RELATIONSHIP OF AGE AND SEX TO FREQUENCY OF NODULARITY IN CLINICALLY NORMAL THYROIDS



Reproduced, by permission, from Mortensen Woolner & Bennett[88]

ingly frequent from the age of puberty onwards. In a more recent study Mortensen, Woolner & Bennett [81] studied 821 glands from persons in whom neither history nor clinical examination had revealed trouble with the thyroid. Fine 2-mm sections of the glands in this series showed nodules to be present macroscopically in 49 5% of cases (12 2% uninodular and 37.3% multinodular) and to develop mainly after puberty.

Wölfler [141, 142] had advanced the theory that these benign tumours arise from embryonic epithelial rests Aschoff [4] also thought that nodules have nothing to do with the problem of endemic goitre, but are indicative of a benign neoplasia, having no connexion with hyperplasia and involution since they differ in structure from the surrounding thyroid tissues and since senile atrophy does not occur in them at the same time as it does in the internodular parenchyma

Taking an opposite point of view, Wegelin [130, 131, 134] argued in favour of a close relationship between these nodules and goitre This view was supported by Rienhoff for the regressive nodule, and by Rice,[103] Rawson,[99] and McGavack [76] for the hyperplastic nodule

These two schools are still in opposition The truth is that the problem of the pathogenesis of the thyroid nodule, even in non-endemic regions, is very complex and is still not understood According to Stanbury,[113] goitre is a constitutional disease in non-endemic regions, appearing for the first time as adolescent goitre and developing in about 25% of cases into toxic goitre.

It has been observed that endemic and, above all, hyperendemic regions are characterized by the early appearance of parenchymatous and colloid nodules before puberty However, progression to toxic goitre has only rarely been observed among the Bantu by Higginson [45] or by the present author [20]

In pre-pubertal children in the large endemic area of the Ueles (North Congo) I have found nodular formations in some 10% of those with glandular hypertrophy. This hypertrophy occurs on the average in 80% of children aged 5-10 In this connexion we may mention Kimball's [53] hypothesis that there is a relationship between pre-pubertal nodules and severe iodine deficiency during pregnancy—a relationship observed solely in hyperendemic areas, apart from a few exceptional cases in low endemic areas. The following example shows that this hypothesis is probably correct

A subtotal thyroidectomy had been performed on a woman with a large fourth-degree colloid goitre, and, as often happens in the less developed countries, the patient did not come back to the clinic for post-operative care. She became pregnant shortly after having been operated upon and returned to the hospital nine months later caesarean section was necessary to deliver the large baby, which weighed 4300 grams (the mother herself weighed only 45 kg) The child, which was born with a nodular hyperplastic goitre, died. Its thyroid gland weighed 7.5 g, had a nodular surface, and was

To sum up, the diffuse form of endemic *goitre in the adult is more* frequently colloid (atrophic) than parenchymatous (hyperplastic). The structure of the diffuse colloid form is of a distinctly follicular type, with preponderance of the macrofollicular component in an abundant loose fibrous connective tissue. Regressive changes in the stroma are, like the circulatory upsets, of little significance

According to Frattini et al[31] histochemical tests indicate lowered metabolic activity, histoautoradiography and radiochromatography reveal the existence of an intense iodine uptake—particularly by the microfollicular areas—and full but lowered secretory activity, with preponderance of the simpler aminoacids (Table II).

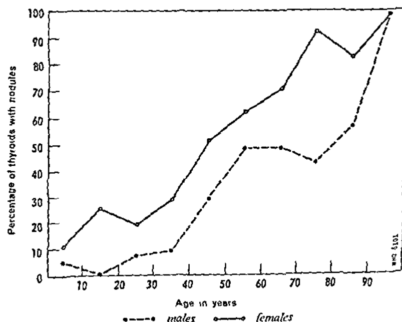
The Thyroid Nodule

Pathogenesis

In the cycle as suggested by Marine,[66] the hyperplastic reaction, at first general, may subsequently become local It takes place in the nodule, this being any macroscopic tumour that can be distinguished from homogeneous thyroid tissue.

During the life of the gland, nodules seem gradually to become more common (Fig. 7) Aschoff[4] and Rice[103] found that nodules were increas-

FIG. 7. RELATIONSHIP OF AGE AND SEX TO FREQUENCY OF NODULARITY IN CLINICALLY NORMAL THYROIDS



Reproduced, by permission, from Mortensen, Woolner & Bennett[85]

FIG 9. AUTORADIOGRAM OF A SECTION OF A NODULAR GOITRE: STAGE 5



Natural size

The white areas are the centres of activity

Taylor's observations support Wegelin's theory that nodules are linked with the pathogenesis of goitre as seen by Marine Nevertheless, it would be premature to discard Aschoff's theory, since undoubted adenomas may develop in the thyroid gland as in any other organ

All these nodules arising by hyperplasia or by involution seem to be associated with goitrogenesis

Wegelin [131] thought that nodules originated as a local reaction to thyroid hormone deficiency Rice's statistics show the presence of regressive and parenchymatous nodules with increasing frequency from puberty onwards and, in exceptional cases, before puberty It is at puberty that thyroid requirements are particularly high

Money & Rawson [79] produced goitre in rats after prolonged administration of thiouracil. They noted at the same time the appearance of a variety of adenomas differing in structure from the goitre caused by thiouracil

We have studied a series of 225 goitres removed surgically in an area bordering on the large hyperendemic area in the Congo. Only 13% of the patients came from a region of low endemicity; the other 87% were from a high endemic area. All the patients but one, a woman with Graves' disease,

microfollicular in type. The woman was given iodine prophylaxis and subsequently gave birth to two normal children

Taylor [119, 120] studied the pathogenesis of the nodules by autoradiography In stage 1, fine uniform mottling indicates homogeneous hyperplasia *of the gland In stage 2, foci appear where the isotope has been taken* up, adjacent to areas where it has not In some subjects all glandular activity may even be concentrated in an area with a picture similar to that of a toxic nodule This is merely a centre of activity in an inactive gland Histologically the epithelium of these active zones is more columnar, with large nuclei

In stage 3, some lobules seem to develop independently of their neighbours, and become hyperplastic to the extent of forming encapsulated nodules which are pathologically distinct from the surrounding tissues Deficient vascularization may lead to necrosis of the centre of the nodule; in this case the picture is one of peripheral activity only (Fig. 8).

FIG. 8 AUTORADIOGRAM OF A THYROID NODULE SHOWING RECENT CENTRAL NECROSIS



Natural size

In stage 4, the nodule becomes cystic, and fills with inactive colloid, or is replaced by new follicles which do not as a rule take up the isotope In stage 5, the process of nodule formation, as described for one lobule, extends to other lobules Here and there a few young stage-2 nodules more or less maintain the euthyroid state of this multinodular form of goitre (Fig. 9).

this series, 31.8% of glands were nodular, and nearly a third of these weighed less than 35 g. In the Congo we have a series of 225 goitres removed surgically, 220 of which are nodular (Table I)

TABLE I FREQUENCY OF NODULES IN THE THYROID GLAND ACCORDING TO DIFFERENT AUTHORS

	Cases	Frequency (%)
Rice,[102] surgery and autopsy	555	56 95
Helwig,[41] autopsy	100	38 2
Nolan,[85] autopsy	725	26.3
Schlesinger et al.,[107] autopsy, nodules measuring 10 mm or more	1313	8 2
Coffey et al.,[13] surgery	431	71.8
Hull,[47] autopsy	221	64 6
Mortensen,[81] autopsy	821	49 5
Tejada,[121] autopsy	279	31 8
De Smet,[21] surgery	225	97 7

For an evaluation of the distribution of nodules in the thyroid, the gland may be divided arbitrarily into five zones (1) the isthmus, (2) and (3) the right lobe, upper and lower segments, (4) and (5) the left lobe, upper and lower segments In our experience, most palpable nodules are localized in the lower part of the right and left lobes It is rarer for the isthmus to contain nodules.

In the Congo we found most nodules in the lower part of the right lobe. These nodules are often pushed towards the mid-line of the neck by the sternocleidomastoid muscle, and present clinically as tumours of the isthmus As a matter of fact, we often found a nodule, commonly a solitary one, originating in the isthmus in semi-cretins and cretinoids.

The predilection of the nodules for the right lobe is explained by Matovinović[72] as resulting from the better blood supply of this lobe, the follicles of this lobe thus receive a larger amount of thyrotropic hormone

The solitary nodule

At autopsies, a solitary nodule has been found in 10%-12% of all thyroid glands[39, 47] and in 17% of glands clinically recognized as nodular

In the surgical series, the figures vary from 25% to 32%[5, 13, 102] In our surgical series in the Congo, we observed only 15% of solitary nodules

Rice[102] found, on histological examination of solitary nodules, that 62% were regressive nodules and 9% were foetal adenomas.

had been operated on for endemic goitre with local complications Among the cases in the endemic area only 18 goitres were diffuse, and had a smooth surface; however, nodules were found in 17 cases on section It appears to us that, in an area without iodine prophylaxis, endemic goitre always becomes nodular after puberty. This strongly suggests that the problem of endemic goitre is associated with nodule formation

Another theory is that of Hull,[47] who found nodules to be most frequent among patients suffering from arteriosclerosis He agrees with Marine and Wegelin that nodules are the result of involution after localized hyperplasia. He believes that cellular hypoplasia is limited at first to some epithelial cells in the follicles, subsequently involves all the cells in one follicle, and finally extends to the epithelium of several follicles, these making up the nodule. The final phase of the regressive process, he believes, is an adenoma containing Hurthle oxyphilic cells

We may note that van Dyke [125] found many more nodules in rats aged 300 days than in those aged 100 days. Attention should also be paid to the observation of Tejada [121] *that nodules are more frequent in undernourished* adults. This phenomenon also suggests the possibility of a regressive process

In conclusion, nodules are seen mainly in endemic areas but also, though less frequently, in non-goitrous areas There are two opposing schools of thought· one explains the pathogenesis of the nodule by Marine's theory *and associates it with goitrogenesis, the other holds that the nodule of* endemic goitre is a separate entity, and associates it with a neoplastic or regressive process. The problem has not yet been solved. As regards the Congo, however, I would stress the fact that the palpable nodule is almost exclusively associated with the endemic state, and is rarely seen in non-goitrous regions.

Frequency and distribution of nodules

Nodules are palpable only when their diameter exceeds about 10 mm. They will thus be found clinically less frequently than at autopsy, where nodules of 5 mm and less can be distinguished. This explains the differences between the statistics of Schlesinger [107] and Hazard & Kaufman,[39] on the one hand, and of Hellwig,[41] Nolan [83] and Mortensen [81] on the other· the last three authors included all nodules, whereas the first three did not take into consideration clinically undetectable nodules with a diameter of less than 10 mm

Another source of statistical divergence is the origin of the series studied The frequency in the surgical series of Rice [102] and Coffey, Amoroso & Mazzara [13] is unduly pronounced because often the aim of their operation was to remove nodular thyroids showing compression symptoms

In tropical countries (such as Guatemala) Tejada [12] examined a series of 279 glands obtained at autopsy from persons over the age of 10 In

to the series of Hull [47] and Mortensen,[81] 64 8% of nodules are of this type; according to our own observations, 46%

Rienhoff,[103] Rice [102] and Fischer [28] considered them to be regressive nodules that have reached the colloid phase in the goitrogenic cycle postulated by Marine [66] The cells are flattened, and all alike The nuclei are small, round, centrally placed and uniform The chromatin is fine, and situated at the edge of the nucleus The follicles are dilated, and sometimes show evaginations; this secondary hyperplasia is a sign of the reaction of some cells to involution.

When these pseudoadenomas have reached a certain stage of development, a capsule forms by compression of the surrounding tissues [18]

Glands containing multiple nodules of the regressive type often proceed to goitrous hypertrophy. In these glands the pseudoadenomas on section are found to contain a brown, gelatinous substance In 13% of cases we observed calcification

The other varieties of nodule on section present as parenchymatous adenomata, while histologically their structure is that of benign tumours Glands with such nodules do not necessarily reach the stage of goitrous hypertrophy.[18]

Wegelin's classification [136] with Rawson's [99] additions is as follows.

(1) The foetal adenoma is comparable to the structure of the thyroid in a chick embryo aged 8-12 days

Wegelin distinguishes a trabecular adenoma in which the follicles have not yet formed—the picture resembles that of a chick embryo of 8-9 days—and a tubular adenoma consisting of narrow tubes without colloid, its structure being comparable to the thyroid of a chick embryo of 10-12 days

(2) The microfollicular adenoma is more differentiated than the tubular adenoma, and the follicles, although below the normal size, are larger and have an epithelium of cubical cells with large nuclei Colloidal secretion is slight This histological picture is also found in the normal thyroid of the premature baby of 8 months and in the newborn, and is comparable to the structure of the thyroid in a chick embryo of 13-15 days (Fig 11)

(3) The mixed micro- and macrofollicular nodule

In this case the regressive phase can be seen along with microfollicles of the hyperplastic phase (see Fig 3, page 322)

(4) The macrofollicular nodule

This is characteristic of the regressive phase (see Fig 6, page 325)

(5) Papillary cystic adenoma

This shows evaginations into the lumen of the cystic follicles It could well be confused with the papillary hyperplastic phase of parenchymatous goitre

We have come across the solitary nodule relatively more frequently in low than in high endemic areas.

The finding of a solitary nodule appears to be of some consequence in temperate regions. In the USA Cope et al [14] report 19% of cancers in solitary nodules as against 10% in multinodular goitres.

Pathology of the nodule

The abnormal growth of the parenchymatous elements of a lobule results in the formation of a homogeneous tumour which stands out sharply against the neighbouring tissues (Fig 10) Macroscopically,

FIG. 10. INVOLUTIVE COLLOIDAL NODULE SHOWING COMPRESSION OF NEIGHBOURING TISSUES WITH CAPSULE FORMATION



its appearance is that of a colloid or parenchymatous adenoma. Under the microscope no lobular structure can be seen. so that it is possible to distinguish this adenoma histologically from normal thyroid tissue. Two main groups of adenoma can be distinguished · the follicular and the foetal.

Most of the nodules observed are of the colloid type These nodules are often well encapsulated, but their histological structure has none of the characteristics of an adenoma. With Fischer,[28] we term them pseudo-adenomas, or follicular adenomas, as opposed to foetal adenomas. According

foetal adenomata are found mainly in regions of moderate endemicity surrounding the hyperendemic zone.

A histological examination of the nodules was made in 173 nodular goitres of our surgical series for the area bordering on the region of high endemicity.

The results were as follows:

	%
(1) Parenchyma:	
foetal adenoma	26
microfollicular adenoma	27
macro- and microfollicular adenoma	23
macrofollicular adenoma	16
mixed cases (showing a mixture of the above varieties)	7
lymphosarcoma or strumitis	1
(2) Connective tissue:	
loose connective tissue	25
connective tissue in fine fibrils	4
sclerosis	20
haemorrhage	19
myxomatous degeneration	11
inflammation	5
hyalinization	6
calcification	9
embryonic rests of keratinized malpighian epithelium	1

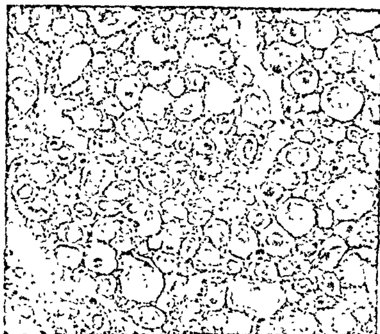
Mortensen, Woolner and Bennett [81] examined the parenchyma and the internodular stroma of glands with nodules in a potentially endemic area. Their findings were as follows.

	%
normal epithelium	3.4
hypertrophied epithelium	1.3
oxyphilic epithelium	0 6
fibrosis	4 9
lymphocytic infiltration	6.5
normal parenchyma and stroma	83 3

Histomorphologically, therefore, the nodular form of endemic goitre presents with a larger number of microfollicular structures than does the diffuse form. The stroma is less abundant, but there are more regressive changes, which are accompanied by parenchymatous haemorrhage and regressive epithelial phenomena, particularly in the nucleus. According to Frattini et al [31] histoautoradiography and radiochromatography indicate intense secretion and complete elaboration of the group of the iodinated amino-acids, above all in microfollicular nodules, with maximum functional capacity in the youngest follicular structures.

The figures given in Table II, from the paper by these authors, make it possible to compare the frequency of the various histopathological features.

FIG. 11. MICROFOLLICULAR ADENOMA OF THE THYROID



×100

(6) Hurthle's oxyphilic adenoma

This has only rarely been observed in endemic goitre, and we have seen only one case among 220 nodular goitres

The term "adenoma", according to some authors, is an uncertain one, and Warren & Meissner [129] have put forward criteria for differentiating between a goitrous nodule and a true thyroid adenoma They maintain that the latter occurs only in a solitary nodule. This criterion is not accepted by Hull [47] nor have I seen evidence to support it I have in fact repeatedly found foetal adenomata side by side with regressive nodules Hull found different varieties of adenoma in 43.7% of nodular goitres; I have done the same in 7% of goitres.

Using histochemical methods, Haley, Dews & Commers [37] tried to throw some light on the problem In the adenoma, they found an increase in the number of pyroninophilic granules resistant to ribonuclease, granules which they did not find in the cells of the goitrous nodule at the simple hyperplastic phase. Thus, there would be two types of nodule tumours (adenomata) and non-adenomatous nodules

The type of adenoma may vary with the region In hyperendemic zones we have found the macrofollicular type predominating, whereas

Development of the nodules of endemic goitre

Benign development

Since the observations of Williams [135,139] on the normal thyroid, it has been known that only a small fraction of the follicles are active. Taylor [118] showed that in non-toxic goitre most of the follicles become permanently incapable of sharing in normal thyroid function and that only a few groups of follicles produce the hormone necessary for the body Dobyns & Lennon [21] showed that this excessive activity of a few follicles in a nodule may lead to haemorrhage and subsequent central necrosis (see Fig 8, page 328); as a result, these active nodules may undergo cystic degeneration. The blood clot becomes organized, and calcium salts may be precipitated later. Finally, the nodule may form a single cyst with indurated and calcified walls

The cysts are important because of their complications :

(1) Mechanical complications: by compressing neighbouring tissues the nodules may cause parenchymatous atrophy with sclerosis Compression of the large vessels may lead to venous congestion, frequently seen after the menopause. Furthermore, about 13% of these growths are retrosternal

(2) The cysts are sometimes the site of haemorrhage

(3) The cysts may be the site of suppuration, a phenomenon which is more frequently seen in hyperendemic zones In the Belgian Congo we found 7 goitrous abscesses in a total of 220 nodular goitres, i.e , in 3 1% *Bacillus pyocyaneus* was isolated in one case, pneumococcus in another In other cases the culture was sterile (Fig 12)

Malignant development

Uehlinger [123] reported that cancer of the thyroid was 10 times more common in Bern (Switzerland) than in Berlin (Germany) or in the USA, stressing thereby the higher frequency of thyroid cancer in endemic, as compared with non-endemic, areas However, Swiss pathologists have described a rather special tumour, the haemangio-endothelioma, which is found mainly in the goitrous regions of Switzerland The malignant tumours which form in the thyroid nodule are largely of this type

Haemangio-endothelioma is not found with the same frequency in the large endemic area of the northern Congo, or in that at the foot of the Himalayas, or in the USA In these regions the frequency of thyroid epithelioma is very low, in the Congo, according to a rough estimate, it affects hardly 1 in a thousand of nodular goitres

Brull [7] found 0 3% of cancers in a series of 4000 goitre cases in Belgium Uehlinger [123] found 21 cancers in a series of 5408 autopsies at Zurich that included 3037 nodular goitres, i e , 0 07% of cancers In the Far East,

TABLE II. PATHOLOGICAL ANATOMY OF ENDEMIC GOITRE*

SECTIONS		Columns of synoptic tables	Diffuse colloid form	Trabeculo-tubular adenomata	Trabeculo-tubulo-microfollicular adenomata	Microfollicular adenomata	Micro-macrofollicular adenomata	Macrofollicular adenomata	TOTAL (endemic goitre)
		^{131}I uptake g min	158 83	36 66	86	217 5	128 33	36 5	110 83
HISTOPATHOLOGY	Epithelial component	Macrofollicles	93 75	6.25	8.33	11 36	50	82 35	36 00
		Normal follicles	68 75	0	25	34 09	75	72 06	49 88
		Microfollicles	50	37 5	72 22	97 72	93 75	38 23	69 91
		Firm bands	15 62	100	94 44	54 54	31 27	16 17	51 72
		Fissural formations	0	25	27 77	18 18	28 12	1 47	10 82
		Endofollicular proliferation	25	0	13 88	18 18	14	30 88	25 39
	Stroma	Loose connective tissue	59 36	93 75	46 85	50	59 36	43 42	61 10
		Hyaline connective tissue	31 25	25	59 36	43 18	43 75	31 57	33 44
		Fibrous connective tissue	62 50	43 75	71.87	75	56 25	75	58 48
		Lymphoid infiltration	15 62	6 25	12 50	11.35	3 12	15 79	9 23
	Regressive changes	Cellular desquamation	15 62	12 50	18 75	9 09	12.50	31.57	17.80
		Nuclear changes	12 50	43 75	37 50	15 90	31 25	22 36	23 32
		Metamorphosis and degeneration	0	31 25	21 87	6 81	18 75	7 78	12.35
		Hyaline change	9 37	25	40 62	43 18	40 62	26 31	30 01
		Fibrous change	50	18 75	62 50	72 72	53 12	64 46	53 08
		Amyloidosis	0	25	0	0	0	5 26	4 32
		Calcification	0	25	6 25	18 18	0	13 15	8 94
		Necrosis	3 12	50	21 87	27 18	15 62	28 18	20 85
	Circulatory changes	Hyperaemia	46 87	31 25	46 87	38 63	37 50	31 57	40 38
		Stasis	37 50	18 75	50	36 36	34 37	31 57	36 93
		Oedema	40 62	62 50	76 85	61.36	53 12	50	50.20
		Haemorrhage	46 87	43 75	40 62	90 90	62 50	69 73	57 76
HISTOCHEMICAL		Dehydrogenase	52 08	75	50	62 50	81 25	48 95	61 63
		Oxidase	53 75	25	43 75	50	62 5	28 12	43 85
		Phosphatase	2 08	0	3 12	4 16	3 12	0 79	2 21
		Plasma	37 50	0	31 25	37 50	31 20	1 20	23 10
		Schiff	58 33	50	43 75	54 16	68 75	39 58	52 42
		Metachromasia	22 19	25	25	37 50	25	1.20	22 76
HISTOAUTORADIOGRAPHY	Localization of ^{131}I	In the colloid	37.50	Not examined	25 00	65 00	33 33	53 12	42 79
		In the epithelium	37 50		62 50	70 00	25 00	34.37	45 87
		In the microfollicles	81 25		81 25	90 00	75 00	59 37	77 37
		In the macrofollicles	25 00		18 25	5 00	33 33	15 62	19 44
CHROMATOGRAPHY		Monoiodotyrosine	83 3	Not examined	60 00	79 1	37 50	62 50	62 50
		Diiodotyrosine	75 00		50 00	68 66	43 75	58 33	58 34
		Thyroxine	41 6		40 00	50 00	37 50	16 68	63 9
		Triiodothyronine	18 6		10 00	25 00	6 25	0	11 46
		Iodides	25 00		30 00	41 6	26 25	8 33	26 66

* Reproduced, by permission, from Fratini et al [31]

These adenomata are recognized to be pre-cancerous.[19] Soetomo[112] found similar formations in Indonesia.

Thus, the malignant development of endemic goitre nodules remains unconfirmed. It has frequently been reported in Switzerland and the USA,[33] but in the tropics it is rare in the endemic regions, perhaps because sufferers from goitre do not live long enough for malignancy to occur

Factors Influencing Structural and Weight Changes in Endemic Goitre

The structural and weight changes of endemic goitre are influenced by several factors.

Iodine prophylaxis

In endemic areas, the thyroid gland in the newborn baby is in the diffuse hyperplastic phase, with well-conserved lobules, but the number of follicles is increased and they contain no colloid The connective tissue is congested, and hyperaemia may be so intense as to cause dyspnoea and endanger the baby's life

During infancy the number of follicles goes on increasing if there is iodine deficiency If the hyperplastic tissues can take up the amount of iodine the gland requires for the production of thyroxine, the hyperplastic phase ceases and the picture is then one of mixed micro- and macrofollicular goitre, with an increase in colloid[133]

As mentioned above, in 1910 the normal child in central Europe was born with a thyroid weighing on the average 5 g, while in adults it weighed from 34 to 41 g, and in old persons from 30 to 32 g[55] Fifty years ago these weights, which would now be considered pathological, were regarded as normal

Since the introduction of iodized salt and the intensification of pre-natal care for mothers, these average weights have gradually decreased and they are still decreasing[127, 133] According to Schamaun[106] and Uehlinger[123] the weight of the thyroid in about 50% of new-born Swiss babies decreased during a recent 10-year period by 3 g or more The frequency of neonatal goitre, with a gland weighing more than 6 g, fell from 42% to 6% during the same period.

The three classes of congenital thyroid hypertrophy distinguished by Wegelin (up to 3 g, from 3 to 6 g, and more than 6 g) have shown a shift towards the left, and the third class has disappeared In particular, the thyroid hyperaemia of the first three days of life described by Wegelin has become less intense, as a result of the iodine administered before birth.[30]

While a return to normal is something that actually occurs in the physiological goitre of puberty in non-endemic regions,[117] it is rare in endemic areas, where iodine prophylaxis should be instituted before the birth of

FIG 12. INFECTED GOITRE WITH SUPPURATING THYROIDITIS



Note the formation of a collateral circulation in the thoracic region as a result of venous stasis.

Ito [48] discovered 40 cancers in examination of 185 nodular goitres. Mortensen et al [80] found 2 1 % of malignant neoplasms in clinically normal thyroids, and 4 2% in nodular thyroids.

It has been generally accepted since Graham [35] that 90% of thyroid cancers develop in an already existing nodule

Ward [128] was the first to doubt the existence of an antecedent benign nodule, a doubt that has since been shared by Lahey & Hare,[57] Meissner & McManus,[77] Swinton,[116] Crile,[17] VanderLaan [124] and Thalmann,[122] who believe that a transition from a benign adenoma to cancer is rare. Reliable evidence is difficult to obtain, since it is usually impossible to prove that the pre-existing nodule was free from malignancy.

It is very probable that many nodules, in particular the solitary ones, are potentially cancerous from the outset Even in the tropics, where epitheliomas are rarer than in temperate climates, we have observed that in endemic zones children before puberty sometimes exhibited solitary nodules that on removal revealed a papilliferous, hyperplastic adenoma.

The gland in adults contains follicles with a diameter of 160-300 microns Among adult subjects in Tejada's series, the thyroid glands showed a decrease in the diameter of the follicles, with little colloid and a fibrous stroma. This might be regarded as premature senile involution.

The role played by hormones

The influence of the folliculin secreted by girls during puberty seems to be more important than increased metabolic activity. This is shown by the greater increase in the size of the thyroid in girls as compared with boys of the same age.[92]

Loeb has reported cyclic hypertrophy of the acinar epithelium during the luteal phase of menstruation Among the Chinese, thyroid hypertrophy was already recognized as a sign of pregnancy several centuries ago.

In a study[20] of the relationship of goitre to gynaecological growths in the endemic and non-endemic areas of the Congo, I found that 7% of women with a goitre also had a uterine fibromyoma This association does not necessarily impair thyroid function in women. In one case of hyperthyroidism, I found on biopsy a gland without histological evidence of hyperthyroidism, instead, the follicles were dilated and well filled with colloid, and the epithelium was normal In this case, the cause was hyperfolliculinism Thyroidectomy aggravated the situation, but subsequent total hysterectomy resulted in cure Thus, in non-endemic areas goitre in women should suggest the *a priori* possibility of some gynaecological condition.

Influence of goitrogens; experimental goitre

Certain thyrostatic substances can cause endemics which are not due to iodine deficiency Endemic goitre occurred during the Second World War in some Belgian convents, and, more recently, as Clements[10, 11] has reported, endemic goitre periodically made its appearance in Tasmania despite regular iodine prophylaxis

These endemic goitres are due to causes other than iodine deficiency, and knowledge of them is important if the problem of endemic goitre is to be understood

1 *Experimental* Research workers have never been able to induce colloid goitre in animals by an iodine-deficient diet, the best experimental

theory is that colloid goitre is only a regressive phase of a previously hyperplastic gland and the succession of hyperplastic and regressive phases gives rise to large goitres Using sulfaguanidine as a thyrostatic, Mackenzie &

the child to prevent nodular hyperplasia and subsequent involution. A return to normal may occur in goitres that are uniformly hyperplastic. Experience has shown that localized changes, such as nodular hyperplasia, hardly respond at all to iodine medication and that usually a remnant of the nodule will be noticeable later.

On the whole, the incidence of the disease among adults in endemic regions has considerably decreased, and palpable nodules do not appear at such an early stage, if at all. On the other hand, thyroid cancer has not decreased, despite the great success of iodine prophylaxis against endemic goitre, only sarcomas and epitheliomas have decreased, whereas certain other large-celled forms have increased [122]

Stein [114] considers iodine to be ineffective in non-endemic regions in cases of microfollicular goitre This is also the opinion of Guinet,[38] who advises against iodine if there is no certainty that the gland is anatomically and functionally able to use it. In such cases thyroxine gives good results.

The role of malnutrition

The influence of malnutrition was studied by Oberndorffer [89] at the end of the First World War, and he held that deficiency states cause different degrees of atrophy in the gland. Hottinger [46] made a similar study during the Second World War, but did not find any significant change in the structure of the thyroid in undernourished prisoners in German concentration camps Furthermore, hepatic cirrhosis often accompanies malnutrition and marasmus, and in 31% of cases thyroid atrophy is observed

The problem was again taken up by Tejada [121] in Guatemala, where the majority of the population suffer from chronic malnutrition in comparison with European standards This author compared a series of 357 thyroids with a series from New Orleans, an area free from goitre, and found differences both in adults and in children However, on comparing the thyroids of Guatemalan children suffering from kwashiorkor and marasmus with those of well-fed children in the same country, he did not find any significant differences. Among undernourished adults he found only a more marked tendency to nodule formation.

Observations during the European wars and in Guatemala therefore do not justify the drawing of any definite conclusion about the influence of malnutrition on thyroid structure

The structural differences between the thyroids of children in tropical countries where malnutrition is prevalent and those of children in temperate countries free from endemic goitre lie in the diameter of the follicles; this averages 36-42 microns in children living in the tropics, whereas in children in the USA it may be as much as 160 microns Interacinar fibrosis is also more marked in young undernourished children in the tropics than in white children, and is found in the liver as well.

The gland in adults contains follicles with a diameter of 160-300 microns. Among adult subjects in Tejada's series, the thyroid glands showed a decrease in the diameter of the follicles, with little colloid and a fibrous stroma This might be regarded as premature senile involution

The role played by hormones

The influence of the folliculin secreted by girls during puberty seems to be more important than increased metabolic activity. This is shown by the greater increase in the size of the thyroid in girls as compared with boys of the same age [92]

Loeb has reported cyclic hypertrophy of the acinar epithelium during the luteal phase of menstruation. Among the Chinese, thyroid hypertrophy was already recognized as a sign of pregnancy several centuries ago

In a study [20] of the relationship of goitre to gynaecological growths in the endemic and non-endemic areas of the Congo, I found that 7% of women with a goitre also had a uterine fibromyoma. This association does not necessarily impair thyroid function in women In one case of hyperthyroidism, I found on biopsy a gland without histological evidence of hyperthyroidism; instead, the follicles were dilated and well filled with colloid, and the epithelium was normal In this case, the cause was hyperfolliculinism Thyroidectomy aggravated the situation, but subsequent total hysterectomy resulted in cure Thus, in non-endemic areas goitre in women should suggest the *a priori* possibility of some gynaecological condition

Influence of goitrogens; experimental goitre

Certain thyrostatic substances can cause endemics which are not due to iodine deficiency Endemic goitre occurred during the Second World War in some Belgian convents, and, more recently, as Clements [10, 11] has reported, endemic goitre periodically made its appearance in Tasmania despite regular iodine prophylaxis

These endemic goitres are due to causes other than iodine deficiency, and knowledge of them is important if the problem of endemic goitre is to be understood

1 *Experimental* Research workers have never been able to induce colloid goitre in animals by an iodine-deficient diet; the best experimental subject still remains man, as put to the therapeutic test of iodine prophylaxis On the other hand, goitre has rapidly been produced in animals by a diet based on goitrogenic vegetables [9, 42], and by thyrostatic drugs [63] Marine's theory is that colloid goitre is only a regressive phase of a previously hyperplastic gland and the succession of hyperplastic and regressive phases gives rise to large goitres Using sulfaguanidine as a thyrostatic, Mackenzie &

Mackenzie[62] produced a colloid goitre in the rat after intermittent administration of this antithyroid compound. The gland remained twice its normal size for a long period. However, simple, irreversible colloid goitre, characterized by distended follicles and a flattened epithelium in the resting stage, has not been obtained.

2. *Histological* Goitres induced in man by treatment with antithyroid compounds are totally different in structure from endemic colloid goitre. The epithelium is cubical with papilliferous evaginations; the nuclei are large, and their abnormal size reveals a state of excitation under the influence of the thyrotropic hormone Colloid is often absent

3 *Epidemic* The concept of goitrogenic substances is useful and perhaps makes it possible to understand the shades of difference in one and the same well-defined endemic zone. Despite a general iodine deficiency, some people have a clearly visible goitre and others, living in the same district, one that is hardly palpable. In the Belgian Congo we suspected that certain antithyroid compounds in the food played a part in the genesis of endemic goitre.[20]

Cretinism

In high endemic areas, cretins are hypothyroid or athyroid and have a larger than normal pituitary.[62] In moderate endemic areas, cretinism is less intense, and semi-cretins and cretinoids present a picture of nodular goitre, the nodule often being solitary Macroscopic examination shows these nodules to be benign tumours, usually fibrous, with a central calcified cicatricial area, or sometimes colloidal cysts with calcified walls Histologically, the foetal and microfollicular forms are those most frequently seen Autoradiography of these nodules sometimes reveals peripheral follicular activity (Fig 13)

Classification of Endemic Goitre

Several classifications of endemic goitre have been suggested, based on somato-clinical, functional and pathological criteria.

1 *For their mass surveys, Perez, Scrimshaw and Muñoz*[85] have proposed a simple and effective somato-clinical classification with the aim of following up the results of iodine prophylaxis in Central America. This classification is on the same lines as the traditional Swiss one.

Group 0 *Thyroid non-palpable or palpable, less than 4 to 5 times the normal weight of the gland for that age.*

Group 1 Goitre palpable and visible when the neck is extended

Group 2 Goitre visible with the neck in any position.

Group 3 Large goitre

FIG. 13. AUTORADIOGRAM OF A FOETAL ADENOMA SHOWING CENTRAL FIBROSIS



Natural size

This system does not take into account glandular consistency or degree of nodularity Moreover, although it is perhaps easily applicable to high endemic areas where early cases can be neglected, it is not suitable for surveys in primary schools in mild endemic areas In these, Group 0 cases call for further subdivision, for some palpable glands in children before puberty are slightly larger than the thumb-nail, with an isthmus exceeding 5 mm in thickness, and have doubled in weight, but have not reached the critical weight for goitre, i e, 4-5 times the normal This is a hyperplastic reaction which warrants attention, since it is not general, the majority of thyroids within normal anatomical limits being impalpable or just about palpable The subsequent discovery of one or more nodules in these larger than normal glands is of great significance, as are also hard glandular consistency and an irregular surface.

Consequently, we have always used a more elaborate system than that of the authors cited above, one which has given us more data for analysis at the end of the surveys Our classification of endemic goitre is as follows

diffuse

(a) diffuse parenchymatous goitre — DP

(b) diffuse colloid goitre — DC

nodular

(a) generalized nodular goitre — NG

(b) 1 localized whole-lobe nodule — WN

2 solitary nodule — SN

The following degrees are distinguished in each class:

0 Impalpable thyroid
I. Palpable thyroid, just visible on swallowing
II. Thyroid visible when neck is extended
III. Goitre visible without extension of neck
IV. Large goitre

Diffuse parenchymatous goitre is only found up to adolescence. It is firm in consistency, smooth in surface, small, regular, and follows the outline of the normal gland. Most schoolchildren with hypertrophy have this type

Diffuse goitre corresponding to the criterion of Perez, Scrimshaw and Muñoz,[95] i.e , with a gland at least 4-5 times the normal size, is found from puberty onwards, or before puberty in hyperendemic zones

Generalized nodular goitre is the prototype of the goitre found in endemic regions.

Solitary nodules are less common, and so are whole-lobe nodules[6] where only one lobe is affected and the other, hardly palpable, is normal. The latter are surgically important

We sometimes distinguish additional characteristics

d descending
a adherent to the skin (indicating infection or subcutaneous haemorrhage from arteriosclerosis)
i infection
h↗ hyperthyroidism
h↘ hypothyroidism

2 Functional classification distinguishes between goitre accompanied by hypothyroidism, euthyroidism, or hyperthyroidism

Cretins, semi-cretins and cretinoids are recognized in high endemic areas by physical and psychiatric examination Some adolescents and adults display marked apathy or hypothyroidism

In most sufferers from goitre, however, thyroid function is normal

Slight symptoms of hyperthyroidism often appear at puberty (parenchymatous goitre) Toxic adenoma (Plummer's disease) is thought to be the end-result of the development of the goitrous nodule. Exophthalmic goitre appears mainly after the menopause, but may develop as a result of excessive intake of iodine by people with a goitre.

3. Aschoff's[4] pathological classification of endemic goitres, based on disorders of function, is still used in Germany:

A. Hyperplasia of the thyroid (diffuse struma)

1. Diffuse parenchymatous goitre of the newborn.[1]

2 Diffuse macrofollicular colloid goitre
   (*a*) proliferating· forms with a hyperthyroid tendency, ranging from the subclinical to the serious;
   (*b*) non-proliferating: euthyroid forms with apathy and hypothyroidism, cretinism
3 Diffuse microfollicular colloid goitre (the normal thyroid of mountainous areas, according to Wegelin)
4 Diffuse parenchymatous goitre of the exophthalmic type with severe hyperthyroidism·
   (*a*) with the triad of exophthalmic goitre,
   (*b*) without the triad of exophthalmic goitre
5 Diffuse colloid goitre of the exophthalmic type

B Adenomatous hyperplasia
6 Diffuse proliferating and non-proliferating nodular colloid goitre with hyperthyroidism or hypothyroidism

C. Adenomatous form
7 Simple nodular goitre, hypothyroidism
8 Nodular goitre of the exophthalmic type, hyperthyroidism

Wegelin drew up another pathological classification that is simpler and more generally followed

A. Diffuse goitre
1 Diffuse parenchymatous goitre (microfollicular)
2 Diffuse colloid goitre

B Hyperplastic nodular goitre (nodular hyperplasia)

C. Adenomatous nodular goitre
1 Parenchymatous nodular goitre (trabecular, tubular, microfollicular)
2 Macrofollicular nodular colloid goitre

D Diffuse and nodular goitre (mixed forms)

To sum up, the classification selected should be adequate for the purpose the examiner has in view For medical surveys the doctor needs a simple classification so as to follow up the results of iodine prophylaxis, select cases for surgery, and have some guide, based on nodularity at school age, to the degree to which goitre is endemic, the clinician, being interested primarily in thyroid dysfunction, looks at the problem from the purely practical viewpoint of treating his patients as effectively as possible, while the pathologist in the laboratory, sectioning material obtained at autopsy or after surgical excision, sees the classification as descriptive

REFERENCES

1 Anderson, W A D (1948) *Pathology*, St. Louis, Mosby, p. 1055
2 Andrew, W & Andrew, N (1942) *Amer J Path*, 18, 849
3 Arndt, H J (1931) *Der Kropf in Russland*, Jena, Fischer
4 Aschoff, L (1924) *Lectures on pathology*, New York, Hoeber, p. 313
5 Beal, J, Scholnick, G & Stevens, G (1952) *A.M.A Arch Surg*, 65, 879
6. Blondain, S (1955) *Chirurgie du corps thyroïde*, Paris, Masson
7 Brull, L. (1950) *Rev méd Liège*, 6, 1, 13, 23
8. Cassano, C, Baschieri, L & Adreani, D (1959) *Presse méd*, 67, 681
9 Chesney, A M, Clawson, T. A. & Webster, B (1928) *Bull. Johns Hopk. Hosp*, 43, 261
10 Clements, F W. (1954) *Med J. Aust*, 2, 894
11 Clements, F W (1958) *Bull Wld Hlth Org*, 18, 175 (revised and expanded as the chapter *Health significance of endemic goitre and related conditions* on page 235 of this monograph)
12. Clerc, E (1912) *Frankfurt Z Path.*, 10, 1
13. Coffey, R J., Amoroso, W & Mazzara, R (1950) *Surg. Clin N Amer*, 30, 1693
14. Cope, C et al (1949) *J clin Endocr*, 9, 1012
15 Cowdry, E V (1918) *Contr Embryol Carneg Instn*, 8, 39
16 Cramer, W & Ludford, R J (1926) *J Physiol*, 61, 398
17 Crile, G, jr (1953) *New Engl J Med*, 249, 584
18 Davies, J & Rogers, L (1940) *Brit med J.*, 1, 764
19 Desaive, P (1951) *Rev méd Liège*, 6
20. De Smet, M P (1954) *Ann Soc belge Méd trop*, 34, 47
21 De Smet, M P (1957) *Docum Med geogr trop (Amst.)*, 9, 385
22 De Smet, M P (1958) *L'endémie goitreuse du Congo Nord Communication to the Sixth International Congress of Tropical Medicine and Malaria*, Lisbon, 1958, p 226
23 De Smet, M P & De Visscher, M (1960) *Ann Soc belge Med trop* (in press)
24 Dobyns, B M & Lennon, B (1948) *J clin Endocr.*, 8, 732
25 Dogliotti, G & Nuzzi-Nutti, G (1933) *Arch Sci med*, 57, 641
26 Dogliotti, G & Nuzzi-Nutti, G (1935) *Endocrinology*, 19, 289
27 Eickhoff, W (1958) *Frankfurt Z. Path*, 69, 80
28 Fischer, R (1949) *Helv chir Acta*, 16, 36
29 Fisher, E & Fisher, B (1951) *Amer J Surg.*, 82, 202
30 Fränkel, B. (1951) *Die anatomische Kontrolle der Jodprophylaxe des endemischen Kropfes im Kanton Bern 1946 bis 1950*, Bern (Thesis)
31 Frattini, P G et al (1957) *Rev lyon Méd*, 6, 1143
32 Garau, B (1938) *Endocr pat cost.*, 13, 103
33 Ghigi, C. & Reggiani, E (1939) *Endocr pat cost*, 14, 242
34. Goetsch, E (1916) *Bull Johns Hopk Hosp.*, 27, 129
35 Graham, A (1924) *Surg Gynec. Obstet*, 39, 781
36. Guinet, P (1955) *Presse méd*, 63, 47
37 Haley, H, Dews, G M & Commers, G S (1955) *Arch. Path (Chicago)*, 59, 635
38 Hazard, J. B (1958) *Fed Proc*, 17, No 3, Part II, Suppl No 2, p 95
39. Hazard, J B & Kaufman, N (1952) *Amer J clin Path*, 22, 860
40. [illegible]
41. [illegible]
42. [illegible] ...ia, Lippincott
43 [illegible]
44. [illegible]

45 Higginson, J (1958) *Fed Proc*, 17, No 3, Part II, Suppl No 2, p. 69
46 Hottinger, A et al (1948) *Hungerkrankheit, Hungerödem, Hungertuberkulose*, Basel, Schwabe
47 Hull, O H (1955) *Arch Path Lab Med*, 59, 291
48 Ito, Y. (1952) *Tôhoku J exper. Med*, 56, 133
49. Jackson, J L. (1931) *Anat. Rec.*, 48, 219
50. Jaffe, R. (1930) *Arch. Path (Chicago)*, 10, 887
51. Johnson, N C (1953) *Aust N Z. J Surg*, 23, 95
52 Johnson, N C (1954) *Aust N Z J Surg*, 23, 241
53 Kimball, O P (1958) *Fed Proc*, 17, No 3, Part II, Suppl No 2, p 63
54 King, T W. (1836) *Guy's Hosp Rep*, 1, 429
55 Kloeppel, F. (1910) *Beitr path Anat*, 49, 579
56 Koch, G (1958) *Z Zellforsch.*, 47, 517
57 Lahey, F & Hare, H (1951) *J. Amer med Ass*, 145, 689
58. Lovell, W, Stevenson, G. & Wartman, W. (1956) *A M A Arch Path*, 61, 62
59 Lowe, E (1930) *Quart J micr Sci*, 73, 437
60. Ludford, R J & Cramer, W (1928) *Proc Roy Soc. London*, 104, 23
61. Ludwig, K S. (1951) *Schweiz Z Path*, 14, 322
62. Mackenzie, C G & Mackenzie, J B (1943) *Endocrinology*, 32, 185
63 Mackenzie, J B, Mackenzie, C. G & McCallum, E V (1941) *Science*, 94, 518
64 Major, R H (1909) *Amer J Aust*, 9, 475
65. Marine, D (1922) *Physiol Rev*, 2, 521
66 Marine, D (1924) *Medicine (Baltimore)*, 3, 453
67 Marine, D (1932) *The thyroid, parathyroids and thymus* In Cowdry, E., *Special cytology*, New York, Hoeber
68 Marine, D (1935) *J Amer med Ass*, 104, 2250
69 Marine, D & Lenhart, C. H (1909) *Arch intern. Med*, 4, 440
70 Marine, D & Rogoff, J M (1916) *J Pharmacol exp Ther*, 9, 1
71. Marine, D & Rosen, S H (1934) *Amer J Physiol*, 107, 677
72. Matovinovic, J (1958) *Fed Proc*, 17, No 3, Part II, Suppl No 2, p 61
73. McCarrison, R (1917) *The thyroid gland in health and disease*, London
74 McCarrison, R (1935) *Recent researches on the aetiology of goitre* In *Verhandlungsbericht, Zweite Internationale Kropfkonferenz in Bern, 10-12 August 1933*, Bern, p 354
75 McClendon, J F & Williams, A (1932) *J Amer Med Ass*, 80, 600
76 McGavack, T (1955) *Amer J med Sci*, 230, 15
77. Meissner, W & McManus, R C (1952) *J clin. Endocr*, 12, 1474
78 Modell, W (1933) *Anat. Rec*, 55, 251
79 Money, W & Rawson, R W (1947) Experimental production of thyroid adenoma in the male rat In, Means, J H, *The thyroid and its diseases*, Philadelphia, Lippincott, p 124
80 Mortensen, J D, Bennett, W A & Woolner, L B (1959) *Incidence of carcinoma in thyroid glands* In *American College of Surgeons Proceedings of the Forum Sessions*, vol 5, p 659
81 Mortensen, J D, Woolner, L B & Bennett, W A (1955) *Trans Amer Goiter Ass*, p 346
82 Niépce, B (1851) *Traite du goître et du crétinisme.. dans les departements de l'Isere, des Hautes-Alpes et des Basses-Alpes*, Paris, Bailliere
83 Nolan, L E (1938) *Amer J Path*, 25, 1
84 Nonidez, J F (1931) *Arch neurol Psychiat (Chicago)*, 25, 1175
85 Nonidez, J F (1932) *Anat Rec*, 53, 339
86 Nonidez, J F (1935) *Amer J Anat*, 57, 135
87 Norris, E H (1916) *Amer J Anat.*, 20, 411
88 Norris, E H (1918) *Amer J. Anat*, 24, 443

89 Oberndorffer, F (1918) *Münch med. Wschr*, 65, 1189
90 Oleson, R (1926) *Publ. Hlth Rep. (Wash.)*, 41, 267
91 Oleson, R (1929) *Publ. Hlth Rep (Wash)*, 44, 1463
92 Oleson, R & Taylor, N (1926) *Publ Hlth Rep (Wash)*, 41, 1695, 1881
93. Oleson, R & Taylor, N (1927) *Publ. Hlth Rep (Wash)*, 42, 804
94 Pales, M L (1950) *Presse méd*, 58, 622
95 Perez, C, Scrimshaw, N W & Muñoz, J A (1948) *Bull Wld Hlth Org*, 18, 217 (revised and expanded as the chapter *Technique of endemic goitre surveys* on page 369 of this monograph)
96 Poate, H & Spencer, S L (1945) *Med J Aust.*, 1, 223
97 Ponse, K (1951) *Ann Endocr (Paris)*, 12, 266
98 Porter, K R., Claude, A & Fullam, E F (1945) *J exp Med*, 31, 233
99 Rawson, R W (1948) In Means, J H, *The thyroid and its diseases*, 2nd ed, Philadelphia, Lippincott, p 118
100 Rawson, R W & Starr, P (1938) *Arch intern Med*, 61, 726
101 Rice, C O (1931) *West J Surg*, 39, 925
102 Rice, C O (1932) *Arch Surg (Chicago)*, 24, 505
103 Rice, C O (1938) *Arch Surg (Chicago)*, 36, 96
104 Richard, M (1951) *Schweiz med Wschr*, 81, 869
105 Rienhoff, W F jr (1929) *Arch Surg. (Chicago)*, 19, 986
106 Schamaun, H M (1954) *Helv paediat Acta*, 9, 455
107 Schlesinger, M, Gargill, S & Saxe, I (1938) *J. Amer. med Ass*, 110, 1638
108 Seecof, D P (1925) *Amer J Path*, 1, 295
109 Seecof, D P (1927) *Amer J Path*, 3, 365
110 Sigurjonsson, J (1940) *Studies on the human thyroid in Iceland*, London, Lewis
111 Sigurjonsson, J (1950) *Amer J Path.*, 26, 1103
112 Scet[illegible]mo (1951) In Kouwenaer, W., ed, *Leerboek der Tropische Geneeskunde*, Scheltema
113 Stanbury, J (1958) *Bull N Y Acad Med*, 34, 44
114 Stein, A (1959) *A M A Arch Path*, 67, 168
115 Sunder-Plassmann (1941) *Basedow-Studien*, Berlin, Springer
116 Swinton, N. (1953) *Surg Clin N Amer*, 33, 749
117 Swyngheduw, Gineste & Laine (1942) *Presse méd*, No 44, 601
118 Taylor, S (1952) *Lancet*, 1, 175
119 Taylor, S (1953) *Bull Wld Hlth Org*, 9, 197
120 Taylor, S (1958) *Lancet*, 1, 751
121 [illegible] Part II Suppl No 2, p 66
122 [illegible]
123 [illegible] Suppl No 2, p 63
124 [illegible]
125 Van Dyke, J H (1953) *A M A Arch Path*, 56, 613
126 Vogeler, K (1929) *Arch. klin Chir*, 157, 704
127 Walthard, B. (1952) *Schweiz med Wschr.*, 82, 423
128. Ward, R (1944) *Surgery*, 16, 783
129. Warren, S & Meissner, W A (1953) *Tumors of the thyroid gland* Armed Forces *Institute of Pathology*, F 14-20
130 Wegelin, C (1925) *Wien klin Wschr*, 38 [illegible]
131 [illegible]
132. Wegelin, [illegible] *Berne 24-26 août 1927*, Berne
133 [illegible]
134. [illegible] *[illegible]rtb*, 4, 643
135 [illegible] 62, 1

136 Williams, R G (1939) *J Morph*, 65, 17
137. Williams, R G (1941) *Anat Rec*, 79, 263
138 Williams, R. G (1944) *Amer J Anat*, 75, 5
139 Wilson, G E (1927) *Anat Rec*, 37, 31
140 Wilson, G E (1929) *Anat Rec*, 42, 243
141 Wolfler, A (1880) *Ueber die Entwicklung und den Bau der Schilddruse mit Rucksicht auf die Entwicklung der Kropfe*, Berlin, Reimer
142. Wolfler, A (1883) *Arch klin Chir*, 29, 754

ETIOLOGY OF ENDEMIC GOITRE

JEAN ROCHE * & SERGE LISSITZKY **

The cause of endemic goitre has not been completely determined, and is complicated by the existence of factors varying from case to case Although in some parts of the world endemicity is so high that a very large percentage of the population is affected, in others, on the contrary, only a relatively small fraction of the population is affected, although there is very little difference in living conditions between the two areas It follows that etiological factors that have been shown experimentally to affect thyroid hypertrophy must not be regarded as the only ones involved in human pathology, the influence of multiple factors, some of them undoubtedly unknown, must also be taken into account if the origin of the endemic is to be explained We shall confine ourselves here to reviewing the main discoveries in this field, but before discussing them a few general comments should be made.

General Comments

Goitre is produced by a mechanism in which the anterior lobe of the pituitary is concerned as well as the thyroid gland, which is acted on by pituitary thyrotropic or thyroid-stimulating hormone (TSH). Since the secretion of TSH is regulated by thyroxine and its analogues, thyroid-pituitary interaction dominates the pathogenesis of goitre Decrease in thyroid hormone secretion brings about increased secretion of TSH which, in normal subjects, re-establishes the production of the thyroid hormones and their release into the circulation in normal amounts In turn the thyroid hormones inhibit the production of TSH Such a self-regulating mechanism ensures a physiological balance in the secretory activity of the thyroid only if the latter responds adequately to TSH, which seems to activate simultaneously all stages of the biosynthesis and secretion of the thyroid hormones A permanent falling off in thyroid activity results in hypertrophy

* Laboratoire de Biochimie générale et comparée, College de France, Paris France
** Laboratoire de Chimie biologique, Faculté de Médecine et de Pharmacie, Marseille, France

lems of endemic goitre being forgotten and failures being overlooked — failures that have led to doubt being cast on the part played by iodine deficiency itself in the production of goitre[37] We propose to consider, on the one hand, the evidence for the view that iodine deficiency is an important factor in endemic goitre and, on the other, the evidence that its importance is limited.

Regions where air, water, soil, and consequently foodstuffs are poor in iodine are almost always the site of endemic goitre, and only under rather special conditions does it occur outside regions where the diet is deficient in iodides A paper by Von Fellenberg[108] on the relationship between the iodine content of drinking water and the frequency of endemic goitre in Switzerland typifies this view. The number of people with goitre is about 10 % of the population or less when the water contains at least 1 μg of iodine per litre, whereas it generally exceeds 10% and often reaches 30%-50% or more when the iodine content of the water is of the order of 0 2-2 4 μg per litre As regards the relation between the iodine content of the soil and the frequency of goitre, significant results have been obtained in France, England, Argentina, Central America, Colombia, USA, India, Japan, New Zealand, Switzerland, Venezuela and Yugoslavia Nevertheless, certain discrepancies have been noted in these results[37, 108] In Switzerland, people with goitre form 1% of the population in one valley where the soil contains 11 9 μg I/kg, in other valleys the percentages of goitre patients and the iodine content of the soil, respectively, are 12 1% and 4 9 μg/kg, 56 2% and 0 6 μg/kg; and 61 6%and 1 4 μg/kg Similar findings have been made in England, Argentina, Japan, Holland and the USA,[66, 82] and favour Marine's view that goitre is caused by a relative deficiency of iodine[69] This fact has frequently been confirmed experimentally, but, as remarked by Trotter,[106] significant results have been obtained only recently, when it became possible to keep animals on well-defined diets, completely free from the goitrogenic substances present in some of their natural foods Thus, Axelrad, Leblond and Isler[13] observed marked thyroid hypertrophy in mice receiving an iodine-deficient diet (Remington diet), even when each constituent of the diet was stopped in turn An excess of sodium chloride also causes goitre to appear, but this is probably because of the resultant loss of iodides in the urine, the renal excretion of iodides increasing parallel with that of chlorides However, experimental thyroid hypertrophy caused by iodine deficiency cannot be equated absolutely with human goitre

If iodine is to be attributed a role in the production of human goitre, it should also be shown to be effective in its prevention, and, if irreversible lesions have not appeared, in its cure The administration of iodized salt because of its preventive effect has rightly been advocated for a long time by Marine & Kimball[77] and practical methods of administering it have been outlined by Hollman,[50] Matovinović & Ramalingaswami,[80] and Nicod[83] The first demonstration of its effectiveness was given by Bous-

and hyperplasia of the gland, which, initially at least, are compensatory processes [69] In experimental goitre, no further changes take place. In the endemic disease, however, these reactions are succeeded by regression of the hyperplastic gland (exhaustion atrophy), a phenomenon characterized by the appearance of vesicles full of colloid, with the epithelium in the resting stage. It follows that the etiological study of endemic goitre should take into account disorders in the pituitary secretion of TSH and in the biosynthesis and secretion of the thyroid hormones, as well as the response of the gland to prolonged disturbances of endocrine function.

In the present state of knowledge, it is impossible to undertake an objective study of this scope Consequently, we shall limit ourselves to discussing here those etiological factors which are well defined at the present time, not forgetting that none of them is able by itself to cause endemic goitre to appear or persist, and that this disease should be considered in general to be the result of multiple causes, not all of which have yet been defined The role of nutritional factors in the production of goitre was demonstrated long ago, whereas the part played by other factors remains uncertain, this chapter will be devoted primarily to the former.

Iodine Deficiency and Endemic Goitre

The opinion that endemic goitre is due to, or closely linked with, iodine deficiency is very widely held It is necessary to make clear to what extent this view is correct and to point out that extrapolations of experimental results must be made with caution. Experimental procedures generally bring about rapid hypertrophy of the gland, whereas endemic goitre develops only slowly, the body gradually becoming adapted to a progressive disturbance in hormone secretion. It is significant that, in general, the basal metabolic rate is not lowered in sufferers from goitre,[33] whereas it is in experimental animals fed on goitrogenic foods whose action can be inhibited by iodides [56]

Although attempts to cure goitre with iodine were made by Coindet [23] as far back as 1820, Prévost in 1830 seems to have been the first to attempt to connect endemicity with lack of iodine in drinking water. Chatin,[24] by determining the iodine content of air, water and soil (1850-1854), made a prime contribution towards the demonstration of a relationship between the development of endemic goitre and inadequate iodide intake. Subsequently, many pieces of evidence (mentioned in an important survey by Orr & Leitch [84]) in favour of this relationship were found in clinical medicine. However, it was Baumann's [16] basic discovery in 1896 of the exceptional richness of the thyroid gland in iodine that finally indicated the line research should follow and made it possible to try out treatment and develop a method for the prevention of goitre. The successes achieved in these various fields have sometimes resulted in the complexity of the prob-

tracer dose of Na ^{131}I, in goitre patients the radioactivity of the gland is highest after 6 hours. This rapid uptake is accompanied by an increase in the amount of iodine stored by the gland (24% and 7% respectively among subjects with goitre and normal subjects, in groups studied in the Argentine Andes; 74% and 37% respectively in two groups examined in Venezuela). In endemic areas the daily excretion of iodine is uniformly low (15-40 μg/day), whereas it may often exceed 100 μg in other parts of the same country where the iodine intake in the food is higher. By means of the administration of iodine (150 μg, 500 μg, or 1150 μg/day) to goitre patients it was possible to detect the gradual establishment of a positive iodine balance, starting from an initial state where this balance was negative. It follows that these patients were clearly in a deficiency state and that the avidity of their thyroid gland for iodine was related to this state. On the whole, there are numerous observations that fit in with the theory of the existence of dietary iodine deficiency in endemic goitre, but a direct cause and effect relationship cannot be deduced to the exclusion of all other etiological factors. This reservation is all the more necessary because some people in communities where endemic goitre is very prevalent, living in the same conditions as others with goitre, have no thyroid enlargement, although tests of thyroid function give the same results. Among some non-goitrous subjects in endemic regions extremely low values have been found for protein-bound iodine (PBI) in the blood (1-2 μg/100 ml), which indicates at least exceptional adaptation to marked hypothyroidism. Otherwise, the effectiveness of iodides in controlling endemic goitre does not call for lengthy discussion, since the results obtained a few years ago by Scrimshaw et al.[95] in Salvador and Guatemala supplied particularly convincing proof of it. There is no doubt that iodine deficiency can be an important factor in endemic goitre, but the conclusion that it is the sole cause of the disease has been reached too hastily. Indeed, a number of observations, which we shall discuss later, have established that endemic goitre exists in which this deficiency does not seem to be involved. The preventive action of iodides does not by itself justify the view that lack of iodine is the origin of endemic goitre; it may counterbalance some disturbance of hormone biosynthesis of which thyroid hypertrophy is a long-term consequence. The fact that iodine "leakages" due to some upset in enzymatic dehalogenation of the iodotyrosines in the gland[95, 99, 100] produces the same phenomenon is significant. The complex nature of the various stages of biosynthesis and secretion of the hormones and the existence of a pituitary regulatory mechanism for thyroid function render the latter liable to a variety of disturbances that result in the gradual formation of a goitre. Thus it is not surprising that, the role of iodine deficiency in the production of goitre having once been accepted on the basis both of studies of endemic goitre[69] and of experiments on thyroid hypertrophy in the trout[78] and the dog,[79] much discussion has centred around its importance and its mode of

singault,[22] who showed that a mineral salt reputed to be an effective agent for the cure of goitre in Colombia contained a considerable proportion of iodides. This finding provides a link with age-old empirical practice, and it is now universally accepted that the administration of iodized salt to a community threatened by endemic goitre is the most effective means of prophylaxis. Nevertheless, it does not follow that endemic goitre is caused solely by iodine deficiency, this point will be discussed below. The addition of iodide in a quantity not exceeding normal requirements to the food of persons living in an endemic region is frequently not enough to prevent goitre formation,[37] and this shows the multiplicity of the etiological factors involved Although it is difficult to state the exact iodine needs of human adults (20-40 μg per 1000 calories according to Orr & Leitch,[84] 100 μg per day according to Greenwald [33] and the Nutrition Committee of the British Medical Association, 150-300 μg per day according to the Food and Nutrition Board of the United States National Research Council) it is certain that they increase during pregnancy and lactation. Moreover, milk is poor in iodine (8-12 μg/100 ml for human milk [54]). The thyroid becomes enlarged in pregnant women and the foetus, as well as in nursing mothers and the newborn baby, if the maternal diet does not include an adequate amount of iodine. This hypertrophy rapidly regresses on the administration of iodides, and is not seen at all if iodine is given prophylactically; but the problem remains of the extent to which it is analogous to the initial stage of goitre. Nevertheless, prevention is not uniformly successful As will be seen below, the action of certain goitrogenic thiourea derivatives in food is not inhibited by the ingestion of iodides,[42] so that under conditions where goitre is associated with the consumption of food rich in such substances, it cannot be prevented with certainty by the administration of iodized salt

Important research of another kind carried out on people in areas of endemic goitre has also made clear the importance of iodine in food. The uptake of radio-iodine by the thyroid and its excretion in the urine have been specially studied among various population groups—some affected and others unaffected by endemic goitre—in the Argentine Andes by Stanbury et al.,[98] in Venezuela by M. Roche et al.[93] and in the Belgian Congo by Bastenie et al.[a] It is noteworthy that the uptake of ^{131}I by the gland is much higher in endemic than in non-endemic areas (e.g., averages of 74% as against 37% [93]), and is accompanied by a very low urinary excretion of iodides

Significant facts have been revealed in recent studies of endemic goitre by exploration of thyroid function with ^{131}I. Whereas in normal subjects the maximum thyroid uptake of ^{141}I occurs 24 hours after administration of a

[a] Unpublished papers by Bastenie, P A, De Visscher, A, Beckers, C, Burke, J, Ermans, A M, Galperin, H & van der Schrieck, A G presented at a symposium on endemic goitre in the Belgian Congo held at Brussels on 12 January 1960

L-tyrosine residues whose subsequent iodination produces 3,5-diiodi-L-tyrosine. The two stages in iodine fixation may be controlled by different enzymes The next step consists in the condensation of two 3,5-diiodo-L-tyrosine residues, giving rise to an L-thyroxine residue, and of a 3-monoiodo-L-tyrosine with a 3,5-diiodo-L-tyrosine residue to give a 3,3',5-triiodo-L-thyronine residue The linkage mechanism is still completely unexplained, the possible intervention of one or two distinct enzyme systems being purely hypothetical The greater part of the organic iodine in the gland is stored, in the form of thyroglobulin, in the colloid substance of the thyroid follicles It is still a matter of controversy whether this protein is homogeneous Its iodized amino-acid content, which generally varies only slightly (hormone I/total I=ca 0 3) in the glands of normal subjects, may show considerable variations in certain goitres, indicating a decrease in hormone production The iodinated amino-acids are set free from thyroglobulin by a thyroid protease Thyroxine and 3,3',5-triiodo-L-thyroxine are the only iodinated amino-acids constantly circulating in the blood under normal physiological conditions, L-thyroxine including at least three-quarters of the hormonal iodine Free 3-monoiodo-L-tyrosine and 3,5-diiodo-L-tyrosine are de-iodinated by enzyme action to form L-tyrosine and iodide within the thyroid gland, where the I-ions are again used for a fresh cycle of hormone synthesis. The mechanism governing the passage of the hormones from the gland to the plasma has not yet been investigated experimentally. As regards the metabolic fate of the hormones, this involves successively transport by the blood, penetration into receptor cells, and utilization by the latter The cellular phase of their metabolism is governed by a complex equilibrium between de-iodination and de-amination, followed by decarboxylation of the hormones, on the one hand, and their union with cellular proteins on the other The nature of the mechanisms by which the hormones exercise their specific regulatory effect on cell metabolism has not yet been clearly defined

Our knowledge of the goitrogens is derived from observations linking goitre with the kind of diet given to laboratory animals, or with the administration of certain drugs to man, but only goitrogens in the diet play a part, more or less directly, in the development of endemic goitre However, study of antithyroid drugs has been of considerable importance since it has made it possible to produce experimental goitre at will, to study the action of these substances on the thyroid gland and on thyroid-pituitary relations, and to define the nature of their effects on hormone synthesis It has been shown that one or other of the steps in the latter is liable to be upset, whereas the possible action of goitrogens on the peripheral utilization of the hormones remains hypothetical

Nature and mechanism of the action of antithyroid substances

Two types of antithyroid substances, both goitrogens, may be distinguished in terms of their action on iodine metabolism in the thyroid

action The problem that arises is whether iodine deficiency is the primary factor in endemic goitre and to what extent the action of iodides does not merely reflect the maintenance of the thyroid in its normal state or the restitution of a thyroid function possibly impaired by other endemic factors. Before turning to this problem it is desirable to review what is known about the goitrogenic action of the constituents of various foodstuffs and the antagonistic effect of the iodides on this action in certain cases

Goitrogens

In pharmacodynamics and in therapeutics the term "antithyroids" is applied to a group of substances which, although differing chemically, all inhibit the biosynthesis of hormones by the thyroid gland. This disturbance in hormone formation and secretion results in the development of a goitre without hyperthyroidism The term "goitrogens" is used when it is not the action of the substances on thyroid function that is considered, but merely their anatomical effect Since this is the direct result of the antithyroid action, thyroid enlargement may be considered to be a compensatory process. This process depends upon a decrease in thyroid secretion, leading to an increase in the blood level of pituitary thyrotropic hormone and eventually resulting in the formation of a goitre

It was long considered possible that food factors other than iodine deficiency might play a part in the etiology of endemic goitre, but not until the chance discovery in 1928 of goitre in rabbits fed on cabbage [25] was indisputable proof obtained of their existence. Since then, various goitrogens have been isolated, and their mode of action determined. Before discussing their role as factors in endemic goitre, a brief review of the stages of the iodine metabolic cycle affected by these substances is desirable.

Iodine in the food traverses the gastro-intestinal mucous membrane essentially in the form of inorganic iodides, and it is these which appear in the blood. The I-ions in the plasma are taken up by the normal thyroid gland, which concentrates them in a ratio of about 20 : 1 The mechanism by which the thyroid does this is still unknown, and our lack of knowledge about this first step is all the more prejudicial to an understanding of the etiology of thyroid dysfunction in that certain authors [17, 107] regard iodide concentration as the factor limiting the rate of synthesis of thyroid hormones

Probably the iodide in the gland is oxidized to iodine, I_2, which takes part in the substitution reaction and replaces the hydrogen atoms at the 3- and 5- positions in tyrosine, giving rise to 3-monoiodo-L-tyrosine and 3,5-diiodo-L-tyrosine. No convincing experimental proof of the existence of this process has been given, but it appears likely that a thyroid peroxidase is involved in the oxidation. A number of indirect proofs show that the incorporation of iodine into organic compounds takes place exclusively through the tyrosine residues of thyroglobulin, giving rise to 3-monoiodo-

Experimental study of dietary goitrogens

Following the observation by Chesney, Clawson & Webster [25] that large goitres appeared in rabbits fed almost exclusively on a cabbage diet—an observation confirmed in many other laboratories—[18, 19, 61, 74] it was rapidly established that other vegetables of the genus *Brassica*, such as cauliflower, turnip and Brussel sprouts, have goitrogenic properties.[75] These are revealed by the production of thyroid hyperplasia, usually without any considerable accumulation of colloid Subsequently, Hercus & Purves [47] showed that the ingestion of seeds of vegetables belonging to the same genus (cabbage, rape, and mustard) also produced thyroid hypertrophy in the rat Kennedy & Purves [53] extended this research to cover the seeds of swedes and various other kinds of turnip and cabbage, at the same time establishing that the diet contained sufficient iodine to cover normal requirements The goitrogenic activity of soya flour and oil has been questioned, [15, 39, 88, 96, 112] but McCarrison [62] was able to show in very rigorously controlled experiments that soya and groundnut seeds had a goitrogenic effect on young rats The results obtained by Sharpless, Pearsons & Prato [96] are also significant.

The differences observed from country to country as regards the possibility of inducing goitre by the consumption of cabbage may be explained by variations in the iodine content of the diet Other factors, discussed by Greer,[40] would seem to act by changing the amount of goitrogen produced by the cabbage (*inter alia*, rain, amount of sunlight, nature of the soil) In man, goitre caused by eating cabbage is regarded by certain authors [88] as exceptional, but others [101] consider it of some importance in view of the effects of a diet over-rich in swedes observed in Belgium during the period of wartime food restrictions [15] Greer & Astwood,[39] using a test for the inhibition of the concentration by the thyroid of ^{131}I, confirmed most of the data previously established, including the marked goitrogenic properties of swedes and turnips in man, the more moderate effect of cabbage, spinach, carrots, radishes, and peaches, and the absence of any effect in the case of many other foodstuffs As Greer [40] says, when there is any doubt about the goitrogenic property of a foodstuff the final decision depends on the isolation of an active compound and the study of its antithyroid activity in various animal species

The mechanism involved in the formation of experimental nutritional goitres has been clearly established by Griesbach, Kennedy & Purves,[42] who, on studying the goitre produced by rape seed, showed that iodide does not prevent thyroid hyperplasia in the rat and the rabbit, but that the hyperplasia disappears when the pituitary is excised. The pituitary glands of goitrous animals were hyperactive,[41] and the TSH level became as high as that developing after thyroidectomy [43] These results clearly illustrate pituitary participation in the production of these types of goitre, by bringing

(*a*) the thiocyanates and perchlorates, whose goitrogenic action can be reversed by iodides, indicating that they must inhibit thyroid concentration of iodides;

(*b*) thiourea, thiouracil and its derivatives, numerous other thiocarbamide derivatives (aminothiazoles and mercaptoimidazoles), aniline derivatives (sulfaguanidine, para-aminosalicylic acid, etc.) and numerous polyphenols (resorcinol, phloroglucinol, etc.); all these have a hyperplastic and hypothyroidogenic action which can be reversed by L-thyroxine, 3,3′,5-triiodo-L-thyronine or excision of the pituitary, but not by the administration of large amounts of iodide.

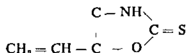
This topic has been discussed at length in general reviews during the last 15 years,[6, 8, 11, 67, 107] ever since the original chance observation by Barker[14] that goitre appeared in patients who had been receiving thiocyanate over a long period for the treatment of hypertension.

The respective properties of these two types of antithyroid substances have been utilized to study separately the concentration of iodide by the gland and its incorporation in thyroglobulin. Thiocyanates and perchlorates do not completely inhibit the penetration of iodide into the thyroid; they appear merely to inhibit the active concentrating mechanism, the nature of which is still completely unknown. The incorporation of iodide in organic compounds is not prevented,[88] the iodotyrosines and thyroid hormones are synthesized normally, but only in small amounts.

Antithyroid substances in the second group, on the other hand, do affect the transformation of inorganic iodide into organic iodide, and many investigations, both *in vivo* and *in vitro*, have clearly shown that these drugs inhibit hormone synthesis. Their mode of action is only partially understood. The theory that it is based on their reducing power[85] has now been abandoned; it would seem more likely that they act as thyroid peroxidase inhibitors.[9] In this way, they would prevent the formation of iodotyrosine residues in the thyroglobulin. It has recently been shown that propylthiouracil also seems to inhibit the iodination of 3-monoiodo-L-tyrosine to 3,5-diiodo-L-tyrosine,[91, 97] probably by an action on iodotyrosine linkage in iodothyronine. In any case, the reduction or inhibition of hormone biosynthesis results in a decrease in the level of circulating hormone and an increase in the secretion of pituitary TSH, giving rise to goitre.

The process outlined above is perhaps over-simplified, for individual factors, as yet little understood, must be taken into account in order to explain the special susceptibility of certain species or individuals to the action of the antithyroid substances. However, it is founded on experimental evidence which has partly served as a basis for the therapeutic use of these compounds, and it does provide an explanation for the pharmacodynamic action of the dietary goitrogens.

in which X may be O, N or S, L-5-vinyl-2-thiooxazolidone also contains this group, having the formula



The mode of action of vinyl-thiooxazolidone is similar to that of thiouracil and its derivatives

Although this compound is widely distributed among the *Cruciferae* liable to cause thyroid hypertrophy when eaten, the existence of other dietary goitrogens must also be considered possible The fact that the absorption of resorcinol applied to skin ulcers has caused goitre with hypothyroidism [21] and that injection into the rat of numerous polyphenols (such as phloroglucinol) inhibits thyroid function [4, 32] has drawn attention to compounds of this type, some vegetables being rich in such substances or in substances that may give rise to them Finally, it is perhaps also necessary to bear in mind the possibility of antithyroid metabolites derived from the normal metabolism of common foodstuffs

The dietary goitrogens and endemic goitre

The observations showing most clearly that the goitrogens in the diet are a definite etiological factor in human goitre are undoubtedly those of Clements [26, 27] and Clements & Wishart [28] These authors showed that in certain parts of Australia and Tasmania, children drinking milk from cows fed on marrowstem kale develop goitres which cannot be prevented by the administration of 10 mg of potassium iodide weekly The presence of a very active goitrogen was demonstrated in the milk of these cows and in the marrowstem kale they eat when thyroid hypertrophy was induced experimentally by adding either the milk or the kale to the diet of calves and rats The uptake of radioiodine by the thyroid gland decreased greatly after consumption of milk from cows fed on this type of kale Finally, Wright [114] recently proved that thiocyanate is present in a high concentration in this milk (about six times as much as in milk from grazing animals) and showed that consumption of the milk leads to the release of radioiodine from the thyroid of rats previously treated with propylthiouracil

Much remains to be done before deciding what importance can be attributed to dietary goitrogenic factors in the etiology of endemic goitre Some of these factors are already known, and although exceptionally they may be held responsible for the appearance of non-toxic goitres in man,[39] it does not seem that, in the immense majority of cases, endemic goitre can be linked with any particular diet Nevertheless, Suk [101] has put forward epidemiological arguments in favour of a relationship between a high consumption of cabbage and endemic goitre in certain villages in the

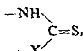
them into close relationship with those produced by the administration of antithyroid compounds.

An important distinction has been established between different types of experimental nutritional goitre: whereas those produced by cabbage [111] and soya [5] regress on the administration of iodide, that produced by rape seed is hardly affected, if at all, by the action of iodide, and only regresses completely after the administration of thyroxine or thyromimetic compounds [87] The analogy with drug-induced goitres produced, on the one hand, by thiocyanates and perchlorates (disappearing after taking iodide) and, on the other, by thiouracil derivatives (responding only to thyroid hormones) is striking, and raises the question of the nature of dietary goitrogens

The existence in cabbage and in the *Cruciferae* in general,[39, 111] of small amounts of thiocyanate or of precursors which can liberate it after enzyme hydrolysis [63] partially accounts, firstly, for the regression of goitre caused by cabbage on administration of iodides and, secondly, for the fact that some workers [63, 76] found it impossible to produce a goitre by the administration of thiocyanate, since this is effective only if preceded by a partial iodine deficiency. The organic cyanides also appear to be goitrogenic by reason of their transformation *in vivo* into thiocyanate

The discovery of dietary and drug antithyroid thiourea derivatives followed that of the goitrogenic activity of phenylthiourea [92] and of allylthiourea.[52] The action of these derivatives is the same as that of the seeds of the *Cruciferae*, it is only partially reversed by iodides and inhibits thyroxine synthesis, as shown by the goitrogenic effect of the hormone and of hypophysectomy [12] This theory has been confirmed by the isolation in 1949 of a very active goitrogen, L-5-vinyl-2-thiooxazolidone (goitrin) from the roots and seeds of the swede and later from the seeds of numerous *Cruciferae*,[10] very recently, the same compound has also been isolated from fresh cabbage leaves.[3] The goitrogenic activity of vegetables containing it is destroyed by cooking. Goitrin exists in the plant in the form of a precursor (progoitrin), the glucoside of L-2-hydroxy-3-butenylisothiocyanate; the release of glucose by enzyme action [7, 39] is thought to bring about immediate isomerization of this compound into goitrin. Perhaps the destruction of the active glucosidase by cooking explains the decrease in the harmful effect of goitrogenic foodstuffs mentioned by Greer [39] and many other authors; on the other hand, the possibility cannot be excluded that cooking promotes the enzymatic breakdown of the active agent by intestinal bacteria

In general, antithyroid activity seems to be exercised by organic compounds containing the group



It is very difficult to assess the importance of nutritional imbalance of the organic constituents of the diet, since it is not always possible to be certain that agents having a pharmacodynamic goitrogenic effect of their own are absent Whereas it has variously been held that excessive or inadequate consumption of foodstuffs rich in lipids, carbohydrates or proteins is responsible in man, better defined diets have been used in experiments on animals

The goitrogenic effect sometimes attributed to excess of carbohydrates appears to be an indirect one which does not call for further consideration, whereas that due to an excess of fats warrants discussion In the past the consumption of lard has been held responsible for endemic goitre in certain parts of the Alps,[94] and the feeding of an excess of oilcake to dairy cows appeared to be connected with thyroid hypertrophy in these animals.[70] Experimental evidence for the goitrogenic effect of fats appears to have been obtained for the first time by Mellanby & Mellanby [81] in the dog However, as butter exerts this effect, whereas cod liver oil does not, its significance has been disputed A number of more recent investigations [89, 90] come out against the existence of a goitrogenic action in dietary lipids It is probable that the findings in its favour are related to a relative iodine deficiency exercising either a direct effect (absence of iodine in butter, presence in cod liver oil) or an indirect one (decreased calcium absorption in the presence of excess fatty acids in the digestive tract) In any case, the practical importance of the role of an abundant dietary fat in producing endemic goitre would seem to be slight, since goitre occurs most commonly in communities whose diet is poor in lipids. Similarly, it is not impossible that under certain conditions the consumption of protein-rich diets may lead to thyroid hypertrophy, but it is unlikely that this can be regarded as an etiological factor in endemic goitre, and the results that have been obtained to this effect in experiments on poultry,[109] rats [110] and mice [52] are difficult to interpret Furthermore, protein deficiency in children is not a factor in thyroid hypertrophy,[104] since this is not usual in kwashiorkor. A more or less acute state of malnutrition is frequently seen in communities where endemic goitre is present, but no cause and effect relationship has beer established for excess or deficiency of a definite energy-giving foodstuff or for a vitamin deficiency The antagonism of vitamin A and thyroxine seems to be of importance only experimentally, and the significance of deficiency in vitamins B_1, C and D, sometimes invoked as a factor in thyroid hypertrophy, is doubtful Malnutrition and nutritional imbalances as such seem to exercise only an indirect effect on endemic goitre, and the findings are contradictory

The only certain relationship that has emerged regarding the favourable or unfavourable action of nutrition on endemic goitre is the effectiveness of iodides as antagonists to certain dietetic goitrogenic factors [20, 53, 55, 62, 111] Thus, iodine prophylaxis retains its value, even if disturbance of thyroid function has some nutritional origin other than iodine deficiency

Carpathians. The appearance of goitre of dietary origin independent of the amount of inorganic iodide added to the diet [28] has been observed only exceptionally. Although it is possible that sporadic goitre may be due to occasional absorption of goitrogenic foods, it is too rare to be of any general etiological interest. Furthermore, a choice between goitrogens and iodine deficiency as etiological factors in endemic goitre is made difficult because of insufficiently extensive epidemiological data, in particular data established on a modern scientific basis. The effects of iodine prophylaxis could indeed be positive even if dietary goitrogens were an etiological factor, since the administration of certain goitrogens in an amount insufficient to block the thyroid can be completely neutralized by simultaneous ingestion of a suitable amount of iodide.[49, 63]

Indirect Nutritional Factors

It would seem that the lack of iodine in certain foods and the presence in others of goitrogens such as L-5-vinyl-2-thiooxazolidone (up to 8 6 g/kg in swedes) may be regarded as important etiological factors in endemic goitre. Where there has been no certainty that such factors are involved, the intervention of other dietary factors has also been postulated. The part that other factors may play remains poorly defined for three main reasons: firstly, the diet of the inhabitants of an endemic region varies from person to person; secondly, nutritional imbalance does not appear to produce thyroid hypertrophy directly but rather to upset iodine metabolism; thirdly, thyroid hormone requirements may differ with the nature and amount of the food consumed, so that iodine requirements may also vary with the diet. The complexity of the problems involved in a study of nutritional factors in endemic goitre other than iodine deficiency and specific goitrogenic agents has been revealed by numerous investigations. It has led to further studies on laboratory animals with the aim of showing experimentally, under more closely defined conditions, the part played by various nutritional imbalances.

The relationship of drinking-water rich in lime to the frequency of goitre has often been pointed out [82] since McClelland's [63] initial work on endemic goitre in Bengal and various Indian provinces. The drinking of hard water and living in regions where the soil is rich in calcium were still regarded recently as important etiological factors in India,[102] whereas this was not thought to be so in Ceylon.[113] To settle this question, it was necessary to tackle the problem experimentally. It was found that only the administration of large amounts of calcium had significant results. A diet relatively poor in iodine is goitrogenic for the rat if it contains an excess of calcium (3 μg I/80 mg Ca/100 g) [46, 105] Calcium is thought to decrease the metabolic effects of thyroxine [1] and would thus appear to exercise an indirect action on iodine deficiency by increasing iodide requirements.[103]

cannot be taken as certain that it is the primary cause of goitre, despite the obvious preventive effect of iodized salt. Dietary, or possibly bacterial, goitrogens exercise a more direct action on the thyroid, inhibiting iodine metabolism in the gland Other dietary factors may complicate the picture, but the role of these factors appears to be a subordinate one In addition, genetic factors may intervene, particularly in regions where endemic goitre has persisted for generations [45] These genetic factors may cause, *inter alia*, a decrease in thyroid functional capacity or faulty renal tubular reabsorption of iodide [23] In this connexion, recent developments in thyroid pathology are very promising, specifically in the field of disturbances in the steps in the utilization of iodine for the biosynthesis of thyroxine and its homologues.[100]

The etiological factors in the production of sporadic goitre are generally regarded as relatively more definite than those of the endemic form We may agree with Trotter [106] that iodine deficiency is the most important of them, whether it is due to inadequate iodide intake or utilization or to iodide leakage, while ingestion of goitrogens and genetic factors are occasional causes The endemic spread of goitre in no way diminishes the possible role of these various factors, although none of them taken separately affords an explanation of the way it spreads in communities

Finally, just as there are cases of rickets resistant to all preventive treatment, in whose production as yet undetermined endogenous factors play a part, so susceptibility to the causative agents of endemic goitre is governed by individual factors which remain unknown

The problems of the etiology of endemic goitre are far from having been solved, but, as Greer said in 1950,[40] very few cases of thyroid hypertrophy not due to iodine deficiency have so far been explained The occasional appearance of endemic goitre during the last thirty years is fairly indicative of the direct or indirect role of iodine deficiency The fact that goitre was unknown until recently in regions where it has since made its appearance has been regarded as evidence against iodine deficiency playing a part in its development [36] Two particularly suggestive observations are at variance with this viewpoint Bastenie et al [a] have reported that in the Belgian Congo a very extensive endemic has developed within the last twenty years or so among the Ueles, ever since the time when these former nomads settled in an area where the water is very poor in iodine. Clements & Wishart,[28] and Clements,[27] whose findings we referred to above, have shown that in some parts of Tasmania the appearance or recrudescence of endemic goitre among children receiving small amounts of prophylactic iodized salt coincided with the school distribution of milk containing a goitrogen ingested by cows fed on marrowstem kale In the first case it would seem that iodine deficiency exerts a direct effect, in the second only an indirect one Known or unknown dietary goitrogens may,

[a] See footnote on p 354

Non-nutritional Factors

The fact that it is in most cases impossible to link endemic goitre with any particular factor in the diet has led, on the one hand, to discussion of the part played by iodine deficiency and, on the other, to consideration of the possible infectious origin of goitre. Important arguments in favour of the latter theory have been put forward by Greenwald,[37] Mc-Carrison [58, 59, 60] and various other authors. Nevertheless, however legitimate the reservations about the theory that lack of iodine in the diet is the cause of endemic goitre, nothing has so far led to the definite identification of non-nutritional factors concerned in the etiology.

Since the pioneer work of Greenwald,[37] advances in the physiology and biochemistry of the thyroid have shown that a relatively high iodine content of the gland is not necessarily incompatible with the existence of goitre. It can no longer be assumed that the hormone level must be closely linked with the total iodine concentration. The absence of a correlation between the iodine content of water and soil on the one hand and the intensity of endemic goitre on the other has been observed, e.g., in England,[35] India,[84] Finland [2] and Norway.[57] Similarly, among neighbouring areas of one and the same country (New Zealand) there may be a larger number of persons with goitre in areas where the soil is richest in iodine.[31] Thus the question was bound to arise whether iodine deficiency is merely a factor in endemic goitre but not its primary cause. The etiological role of infection or toxic post-infectious states was suggested in an attempt to solve this problem

The work of McCarrison et al.[58, 59] on endemic goitre in the Himalayan areas of India drew attention to the importance of water pollution. The appearance of thyroid hypertrophy after experimental pollution of drinking-water was noted by these authors during these classic experiments In addition, the substitution of unpolluted water for drinking-water polluted with human and animal excrement is said to have been followed by the disappearance of endemic goitre from an Indian community.[60] Hettche [43] considers that the active agent is a derivative of the urochrome type, present in the water of endemic regions, and that its action, from the pathogenic viewpoint equivalent to that of a bacterial goitrogen, can be prevented by the simultaneous ingestion of iodide. Other authors believe that a thyroid infection lies at the origin of the goitre [30, 36] The results of their investigations do not carry conviction; nevertheless, the production of a goitrogenic agent *in situ* is a possibility which cannot be excluded.

General Conclusions

The etiology of endemic goitre involves many factors, whose nature and mode of action have not been completely defined. It is certain that iodine deficiency in the diet plays an important part in most cases, but it

27 Clements, F W. (1958) *Bull Wld Hlth Org*, **18**, 175 (revised and expanded as the chapter *Health significance of endemic goitre and related conditions* on page 235 of this monograph)
28 Clements, F W & Wishart, J. W. (1956) *Metabolism*, **5**, 623
29 Coindet, J F. (1820) *Ann Chim Phys*, **15**, 49
30 Crotti, A (1927) In' *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 371
31 Dhole, R A & Andrew, R C (1934) *Dept. of Health and Scient Res Bull*, **45**, 50
32 Doniach, I & Fraser, R (1950) *Lancet*, **2**, 855
33 DuBois, E F (1936) *Basal metabolism in health and disease*, Philadelphia, Lea & Febiger
34 Goldberg, R C & Wolff, J (1954) *Endocrinology*, **54**, 181
35
36
37
38 Greenwald, I (1956) *Amer J clin Nutr*, **3**, 215
39 Greer, M A & Astwood, E B (1948) *Endocrinology*, **43**, 105
40 Greer, M A (1950) *Physiol Rev*, **30**, 513
41 Griesbach, W R (1941) *Brit. J exp Path*, **22**, 245
42 Griesbach, W E, Kennedy, T H & Purves, H D (1941) *Brit J exp Path*, **22**, 249
43 Griesbach, W E & Purves, H J (1943) *Brit J exp Path*, **24**, 174
44 Halverson, A W, Zepplin, M & Hart, E B (1949) *J Nutr.*, **38**, 115
45 Hazard, J B (1958) *Fed Proc.*, **17**, 95
46
47
48
49
50
51
52 Kennedy, T H (1942) *Nature (Lond)*, **150**, 233
53 Kennedy, T H & Purves, H D (1941) *Brit J exp Path*, **22**, 241
54 Leipert, T (1934) *Biochem Z*, **270**, 448
55 Levine, H, Remington, R E & Kolnitz, H von (1933) *J Nutr*, **6**, 325
56 Levine, H, Remington, R E & Kolnitz, H von (1933) *J Nutr*, **6**, 347
57 Lunde, G (1935) In *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 585
58 McCarrison, R (1906) *Lancet*, **1**, 1110
59 McCarrison, R (1908) *Lancet*, **2**, 1275
60 McCarrison, R (1927) *Brit med J*, **1**, 94
61 McCarrison, R (1931) *Indian J med Res*, **18**, 1311
62 McCarrison, R (1933) *Indian J med Res*, **20**, 957
63 McCarrison, R (1933) *Brit med J*, **2**, 671
64 McCarrison, R, Nenrotnb, C, Visvanath, B & Norris, R V (1927) *Indian J med. Res*, **15**, 207
65 McClelland, J (1835) *Trans med phys Soc Calcutta*, **7**, 145
66 McClendon, J F (1939) *Iodine and the incidence of goiter*, Minneapolis, University of Minneapolis Press
67 McGinty, D A (1949) *Ann N Y Acad Sci*, **50**, 403
68 Mackenzie, C G (1947) *Endocrinology*, **40**, 137
69
70
71
72
73 90

because of their action on the biosynthesis of thyroid hormones, cause an increase in iodine requirements and so play an important etiological role in endemic goitre. In the present state of knowledge the primary importance of iodine deficiency cannot be denied, whatever its mode of action—inadequate supply of iodide to the gland or faulty utilization of iodide. To accept this is not to extend experimental results to clinical research indiscriminately, but merely to co-ordinate one with the other.

Endemic goitre necessarily involves alteration in thyroid iodine metabolism *and a group of processes tending to compensate for this. Although* various factors, including the consumption of goitrogenic products, may directly impair thyroid function, the origin of endemic goitre remains indefinite. It may be asked whether different causes do not produce the same effects through the essential intermediary of a faulty supply of iodine to the thyroid for hormone synthesis; this could then be accepted as the immediate cause of the development of goitre, as put forward by Marine,[72] without prejudice to the question of the primary cause, which lies at the origin of the disease.

REFERENCES

1 Abelin, J (1928) *Biochem. Z.*, 199, 72
2 Adleraentz, E (1928) *Act med scand*, 69, 1
3. [illegible] 231, 1817
4 [illegible]
5 [illegible]
6 [illegible]
7 [illegible]
8 [illegible]
9 [illegible]
10 [illegible]
11 [illegible]
12 [illegible] 10
13 [illegible]
14 [illegible]
15 [illegible]
16 Baumann, E (1896) *Z physiol Chem*, 21, 319
17 Berson, S. A & Yalow, R. S (1955) *J clin. Invest*, 34, 186
18 Bianchi, G. C (1933) *Beitr. path Anat*, 90, 539
19. [illegible] 10, 19
20 [illegible]
21 [illegible]
22 [illegible]
23 [illegible] *istopat clin ter.*, 3, 253
24 [illegible]
25 [illegible] *Johns Hopk. Hosp*, 43, 261
26 Clements, F. W (1954) *Med J. Aust*, 2, 894

TECHNIQUE OF ENDEMIC GOITRE SURVEYS

CARLOS PÉREZ, M D.,* NEVIN S SCRIMSHAW, PH.D., M D, M.P.H.** & J. ANTONIO MUÑOZ, M.D , M P H ***

This chapter has been planned for the specific guidance of the physician who wishes to carry out surveys to determine the prevalence of endemic goitre in a population. It is not designed for the clinician studying goitre under hospital conditions where special methods may be required The suggestions made have proved practical and useful under a wide variety of conditions, and the procedures will result in data which can be used with confidence to guide public health programmes

In a survey various types of goitre may be encountered Goitres are classified according to both physiological and morphological characteristics. Their division into " toxic " and " non-toxic " is entirely functional " Toxic goitres " are characterized by an increased output of thyroid hormones into the blood-stream and are important to the clinician because of their dramatic manifestations and the consequences that they may have upon the life of an individual In field surveys " toxic goitres " are hardly ever seen, though some of the signs such as exophthalmus and fine tremor could theoretically lead to the discovery of an occasional case in the field

The " non-toxic " or endemic goitres usually present no dramatic symptoms and are frequently ignored by the goitrous person, except when they are disfiguring or produce mechanical interference with respiration. They represent a hypertrophy of the thyroid due to insufficient iodine, and indicate the prevalence of an absolute or relative deficiency of iodine in a population These non-toxic or endemic goitres may appear at different ages according to the severity of the deficiency A mild degree of deficiency may not become evident until there is an increase in the physiological requirement for iodine During adolescence, particularly in girls, a signi-

74. Marine, D, Baumann, E. J & Cipra, A (1929) *Proc. Soc. exp Biol (N Y.)*, 26, 822
75 Marine, D, Baumann, E. J, Spence, A W & Cipra, A. (1931) *Proc. Soc exp. Biol (N Y)*, 29, 772
76 Marine, D, Baumann, E. J, Webster, B. & Cipra, A (1930) *Proc. Soc. exp. Biol (N Y)*, 27, 1025
77 Marine, D & Kimball, O. P (1921) *J Amer med Ass*, 77, 1068
78 *Marine, D & Lenhart, C H (1909) Arch intern Med*, 4, 253
79. Marine, D & Lenhart, C H (1910) *J. exp Med*, 12, 311
80 Matovinović, J & Ramalingaswami, V (1958) *Bull Wld Hlth Org.*, 18, 233 (revised and expanded as the chapter *Therapy and prophylaxis of endemic goitre* on page 385 of this monograph)
81 Mellanby, E & Mellanby, M (1921) *J Physiol (Lond)*, 55, vii
82 Murray, M M, Ryle, J A, Simpson, B W & Wilson, D C. (1948) *Thyroid enlargement and other changes related to the mineral content of drinking water*, Medical Research Council Memoir No 18, London
83 *Nicod, J L (1953) Bull. Wld Hlth Org*, 9, 259
84 Orr, J B & Leitch, I (1929) *Spec Rep Ser. med Res Coun (Lond)*, No. 123
85 Pitt-Rivers, R (1950) *Physiol Rev*, 30, 194
86 Pitt-Rivers, R, Galton, V A. & Halmi, N F. (1958) *Endocrinology*, 63, 699
87 Purves, H D. (1943) *Brit J exp Path*, 24, 171
88 Rawson, R, Hertz, S & Means, J H (1943) *Ann intern Med*, 19, 829
89 Remington, R E (1938) *J Nutr.*, 16, 417
90. Remington, R E & Harris, P L (1943) *J Nutr*, 25, 203
91 Richards, J B & Ingbar, S H (1959) *Endocrinology*, 65, 198
92 Richter, C P & Klisby, K H. (1941) *Proc Soc. exp. Biol (N Y)*, 48, 684
93 Roche, M, De Venanzi, F, Vera, J, Coll, E, Spinetti-Berti, M, Mendez-Martini, J, Gerardi, A & Forero, J (1957) *J clin. Endocr*, 17, 99
94 Saint-Lager, J (1867) *Etudes sur les causes du crétinisme et du goitre endemique*, Paris, Baillière
95 *Scrimshaw, W S, Cabezas, A, Castillo, F & Mendez, J (1953) Lancet*, 2, 166
96 Sharpless, G R, Pearsons, J & Prato, G S (1930) *J Nutr*, 17, 545
97 Slingerland, D W, Graham, D E., Josephs, R K, Mulvey, P F jr, Trakas, A P & Yamazaki, E (1959) *Endocrinology*, 65, 178
98 Stanbury, J B, Brownwell, G L, Riggs, D S, Perinetti, H, Itoiz, J. & Castillo, E.B del (1954) *Endemic goiter The adaptation of man to iodine deficiency*, Cambridge, Mass, Harvard University Press
99. Stanbury, J B, Ohela, K & Pitt-Rivers, R. (1955), *J clin Endocr*, 15, 54
100 Stanbury, J B & Querido, A (1956) *J clin Endocr*, 16, 1522
101 Suk, V. (1931) *Anthropologie (Praha)*, 9, No 1, p 1
102. Stott, H & Gupta, S P (1934) *Indian J med Res*, 18, 1059
103 Taylor, S (1954) *J clin Endocr*, 14, 1412
104 Tejada, C (1958) *Fed Proc*, 17, Suppl No 66
105 Thompson, J (1933) *Arch Path (Chicago)*, 16, 211
106 Trotter, W R (1959) *In* Pitt-Rivers, R & Tata, J, *The thyroid hormones*, London, Pergamon press, p 159.
107. VanderLaan, W P & Storrie, W. M (1955) *Pharmacol Rev*, 7, 301
108 Von Fellenberg, T (1933) *Mitt Lebensmitt Hyg*, 24, 123
109 Watson, D C (1905) *Lancet*, 1, 74
110 Watson, D. C (1905) *J Physiol (Lond)*, 32, 16
111 Webster, B & Chesney, A M. (1928) *Bull Johns Hopk Hosp*, 43, 291
112 Wilgus, H S, Gassner, F X, Patton, A R & Gustavson, R. G (1941) *J Nutr*, 22, 43
113. Wilson, D C. (1954) *Brit J Nutr.*, 8, 90
114 Wright, E. (1958) *Nature (Lond)*, 181, 1602

On the other hand, in persons with very thin necks the lobes of the gland can be readily seen and may give the impression of a visible goitre, even though the thyroid is actually not more than 4 to 5 times its normal size. A similar false impression may sometimes be given by the configuration of the larynx and trachea in a person with a thin neck. Furthermore, glands with nodules are frequently discovered by palpation which would be unnoticed if the neck were only inspected.

The criterion for the diagnosis of goitre should be the determination of the degree of enlargement or the presence of nodules in the gland and not simply its visibility. The use of the palpation method, therefore, is recommended as the most accurate and reliable way of diagnosing the severity of endemic goitre. Fortunately, palpation does not add appreciably to the time required for each examination. On the contrary, palpation frequently permits the prompt resolution of doubts as to the size of the thyroid—doubts which would require more time to resolve by inspection alone.

It has been suggested that the prevalence of visible goitre bears a fairly constant relationship to the prevalence of goitre diagnosed by the palpation technique, so that if the former is known the latter can easily be inferred. However, studies made by INCAP (unpublished data) in the five countries of Central America and in Panama have shown clearly that such a relationship is not always constant, but varies from one region to another. In areas where the prevalence of visible goitre is high, the additional goitres detected by palpation will not greatly change the interpretation of the over-all prevalence reported. Where the prevalence of goitre is low, however, the detection of glands more than 4 to 5 times enlarged, but still not readily visible, may affect the conclusions drawn by public health authorities as to the magnitude of the problem. The fatness or thinness characteristic of the population and the general shape of the neck will greatly influence the correlation between visible and palpable goitre

Significance of Non-visible Goitre

In the majority of countries in the world there are areas commonly recognized as goitrous owing to the high prevalence of visible goitre, too large to escape the notice of even the casual visitor In such cases it is frequently assumed that the rest of the country is relatively free from endemic goitre However, careful surveys, especially those employing the palpation method, usually show such a belief to be erroneous by revealing a high goitre rate in many zones where the disease was previously unsuspected. For example, this has proved to be true in each of the Latin American countries where nation-wide surveys have been carried out [5]

From a public health point of view, the prevalence of goitre which is readily palpable but not readily visible with the head in normal position may be of great importance The following reasons reinforce the recom-

ficant increase in the number of hyperplastic glands appears in endemic regions. This so-called "adolescent" goitre is not a normal physiological phenomenon but a reflection of an iodine deficiency which has become manifest owing to an increased demand of the body for iodine. Goitres frequently appear during pregnancy and lactation for the same reason.

When the lack of iodine is more severe, endemic goitre may appear very early in life. The pathology of goitres in infants and young children does not differ from those in older children and adults. All start with hypertrophy and hyperplasia of the acinar cells within the follicles. As the deficiency of iodine persists, some of the cells atrophy and the follicles fill with colloid substance. It is the first stage in the development of a colloid goitre, which may later develop fibrosis and become irreversible. This type of goitre is functionally non-toxic and anatomically without nodules and is referred to as *simple* or *diffuse goitre*.

In areas where iodine deficiency has long been present, goitres with adenomatous nodules of varying size may appear. When this occurs, the name *adenomatous* or *nodular goitre* is employed. Functionally, such goitres usually remain non-toxic.

The determination of the prevalence of endemic goitre in a population gives a good appraisal of the severity of iodine deficiency without the necessity of considering the functional status of the thyroid. A prevalence of endemic goitre greater than 10% is almost universally considered to constitute a public health problem. Many authorities feel that a goitre rate above 5% should be considered of public health significance. The goal of the endemic goitre survey sponsored by public health authorities is the determination of the existence and degree of the goitre problem in the population under their care

Methods employed in Goitre Surveys

The methods of carrying out goitre surveys have shown considerable variation in different parts of the world. Many authors advocate the palpation of the thyroid of every person included in the survey. Some use palpation only when visible glands are present in order to determine the anatomical characteristics of the goitre Still others advocate only inspection of the neck, and a few have gathered their information by questionnaires alone.

It is recommended that a gland be classified as positive for goitre only when it is 4 to 5 times larger than the normal size Adenomatous nodules in the parenchyma should be noted regardless of the size of the thyroid When the neck is short or the muscles are well developed, inspection alone may fail to reveal a gland that is already 4 to 5 times enlarged. This may occur also when there is a thick layer of adipose tissue or when the goitre is retrosternal.

On the other hand, in persons with very thin necks the lobes of the gland can be readily seen and may give the impression of a visible goitre, even though the thyroid is actually not more than 4 to 5 times its normal size. A similar false impression may sometimes be given by the configuration of the larynx and trachea in a person with a thin neck. Furthermore, glands with nodules are frequently discovered by palpation which would be unnoticed if the neck were only inspected.

The criterion for the diagnosis of goitre should be the determination of the degree of enlargement or the presence of nodules in the gland and not simply its visibility. The use of the palpation method, therefore, is recommended as the most accurate and reliable way of diagnosing the severity of endemic goitre. Fortunately, palpation does not add appreciably to the time required for each examination. On the contrary, palpation frequently permits the prompt resolution of doubts as to the size of the thyroid—doubts which would require more time to resolve by inspection alone

It has been suggested that the prevalence of visible goitre bears a fairly constant relationship to the prevalence of goitre diagnosed by the palpation technique, so that if the former is known the latter can easily be inferred However, studies made by INCAP (unpublished data) in the five countries of Central America and in Panama have shown clearly that such a relationship is not always constant, but varies from one region to another. In areas where the prevalence of visible goitre is high, the additional goitres detected by palpation will not greatly change the interpretation of the over-all prevalence reported. Where the prevalence of goitre is low, however, the detection of glands more than 4 to 5 times enlarged, but still not readily visible, may affect the conclusions drawn by public health authorities as to the magnitude of the problem. The fatness or thinness characteristic of the population and the general shape of the neck will greatly influence the correlation between visible and palpable goitre.

Significance of Non-visible Goitre

In the majority of countries in the world there are areas commonly recognized as goitrous owing to the high prevalence of visible goitre, too large to escape the notice of even the casual visitor. In such cases it is frequently assumed that the rest of the country is relatively free from endemic goitre However, careful surveys, especially those employing the palpation method, usually show such a belief to be erroneous by revealing a high goitre rate in many zones where the disease was previously unsuspected. For example, this has proved to be true in each of the Latin American countries where nation-wide surveys have been carried out.[5]

From a public health point of view, the prevalence of goitre which is readily palpable but not readily visible with the head in normal position may be of great importance. The following reasons reinforce the recom-

mendation that both palpation and inspection should be used in carrying out goitre surveys:

1. It is most convenient to carry out mass surveys in schoolchildren However, large visible goitres are usually much less prevalent in children than in the adult population, although the total prevalence of enlarged thyroid is more clearly comparable. Palpable goitres in children, therefore, must be recorded in order to obtain an accurate indication of the total goitre prevalence in the whole population.

2. If the attempt is made to measure the effectiveness of iodization programmes by the changes in the size and frequency of visible goitres, two problems are encountered. Many of the goitres are fibrotic and will change very little in size even under optimum treatment, and it is almost impossible to evaluate subjectively by inspection the changes in size of a relatively large thyroid On the contrary, if the criterion for evaluating the response to iodine administration can be the disappearance of the goitre, the task becomes feasible. Most of the diffuse goitres in children which are palpable but not visible with the head in normal position will no longer be present after relatively limited periods of adequate iodine administration.[8]

3. It should be noted that in a population in which goitre is moderately prevalent, but in which most of the glands are not of a large size, the failure to include palpable goitre could lead to the false conclusion that goitre was not sufficiently prevalent to be of public health consequence. This is, of course, particularly true in cross-sectional samples with large numbers of children, but it may also apply to adult populations

4 Adenomatous goitres in children are usually detectable only by palpation. It has been suggested that adenomatous goitres during childhood are strong presumptive evidence of an iodine deficiency in the mother that was particularly manifest during the stress of pregnancy (O P. Kimball —personal communication, 1951).

Assessment of Size of Gland

The normal size of the thyroid varies with the age and build of the individual. In the adult, the lobes are stated to have the size of a lima bean with the isthmus appearing as a thin connecting strand. The gland has a rather firm consistency, is slightly compressible, and presents a smooth surface. On palpation the lateral lobes can be felt beneath the muscles on both sides of the trachea. The isthmus is either not palpable or can just barely be detected.

As stated previously it has been found practical for survey purposes to list as positive for endemic goitre a gland estimated to be more than 4 to 5 times the normal volume. To avoid exaggerating the prevalence recorded, doubtful cases of enlarged glands should be classified as normal. These pro-

cedures will give a very conservative estimate of the prevalence of endemic goitre, but one in which few normal cases will be erroneously included.

It should be noted that, in any field examination, no matter what criteria are adopted a certain percentage of the cases will be border-line. It has been found in practice that if the experience and training of two different observers are similar, they will make different decisions as to the classification of many of the individual border-line cases and yet arrive at approximately the same average goitre rate In other words, the variations in assigning border-line cases to either the normal or the positive category tend to be random for most observers

Any attempt to define the normal thyroid gland in terms of an arbitrary standard tends to break down in actual practice. However, persons carrying out field surveys soon become familiar with the size of the thyroid in individuals of varying ages and body build through examinations of populations with little or no goitre For North American adults the size of a large lima bean has been suggested as a standard for comparison. This obviously does not apply to young children and, furthermore, lima beans are different or unknown in many parts of the world The FAO/WHO Third Conference on Nutrition Problems in Latin America, held in Caracas, Venezuela, in 1953, met this problem by suggesting that the dimensions of the thumb nail of the person being examined be used as an approximate reference [2] In this case the thumb nail must be visualized as outlining the size of a kidney-shaped bean Usually a thyroid gland whose lateral lobes have a volume greater than the terminal phalanges of the thumbs of the person being examined will be considered goitrous For many persons, the size of the lateral lobes may be more easily visualized in comparison with the terminal phalanx of the thumb than as an arbitrary multiple of a normal standard

These comparisons have all proved of practical value in training new survey workers It should be emphasized, however, that only as the examiner becomes accustomed to estimating thyroid volume by palpation do reference standards become really meaningful By this time these " standards " have become merely useful adjuncts and are no longer employed uncritically

Technique of Examination

The technique varies slightly according to the age of the subject Children and adults are examined while standing with the head and neck in a vertical position. According to the height of the individual the examiner sits or stands directly in front of the subject. He examines the thyroid area and without delay uses both thumbs simultaneously to examine very gently the full extent of the lobes and the isthmus (see Fig. 1) It is advisable to ask the patient to relax the neck muscles by throwing the head slightly downwards, and it may be helpful to get him to swallow several times

For the clinical appraisal of patients most physicians advise examination from behind with the forefingers as the most accurate and reliable method for the palpation of the thyroid gland. However, for general survey work it is more convenient to adopt a position in which inspection and palpation can be carried out almost simultaneously without requiring the patient to turn around. Such a procedure is much better adapted to the rapid examination of lines of people. The examination from behind with the forefingers can still be resorted to in those relatively few cases where extra sensitivity on palpation is required.

For infants, Eggenberger's technique is recommended.[1] The child lies on his back, and the left hand of the examiner is placed on his shoulder-blades, lifting him slightly so that his head remains in touch with the surface of the table on which he is lying. The body of the child can be securely held by placing the thumb of the left hand in his right armpit. The region of the thyroid is then palpated with the forefinger. The gland should not be palpable and the isthmus should be palpable only as a thin strand, not more than 1 to 2 mm thick.

Classification of Goitres[a]

Many different criteria have been employed for the classification of the various degrees and kinds of goitre. The need for unifying the criteria used in endemic goitre surveys is evident, especially when several surveys done at different times by different examiners may be used to draw conclusions about the effectiveness of prophylactic measures. Most classifications distinguish between visible and palpable goitres, and the presence or absence of nodules is recorded Visible goitres, as a general rule, indicate a moderate to severe deficiency of iodine of relatively long duration. Visible goitres

[a] This question is discussed in greater detail in the chapter *Pathological anatomy of endemic goitre* by De Smet (p 315)

FIG. 1. TECHNIQUE USED IN EXAMINATION OF THYROIDS

Sitting or standing facing the patient, the examiner places his thumbs gently on either side of the thyroid area and determines the size of the gland by palpation

FIG. 2. GROUP 1 THYROID GLAND

This gland was readily palpable with the head in normal position but was not visible. It is readily visible with the head fully extended

FIG. 3. GROUP 2 THYROID GLAND

This gland is readily visible with the head in normal position.

FIG. 4. GROUP 3 THYROID GLAND

This gland is so greatly enlarged as to be readily visible as a prominent goitre at a considerable distance.





2





4

thus have a tendency to be common among older people, and their presence in children suggests a particularly severe deficiency of iodine Similarly, nodules are likely to be present to a significant degree only in areas where a marked deficiency of iodine has been long standing

The following classification represents a synthesis of the various suggestions put forth by international groups Every effort has been made to present a classification in terms which are as practical and universally acceptable as possible It has proved to be workable in extensive field studies in a number of countries.

Group 0 persons without goitre By definition these are taken to be persons whose thyroid glands are less than 4 to 5 times enlarged.

Group 1 persons with palpable goitres The thyroid is considered to be more than 4 to 5 times enlarged although not visible with the head in normal position Most of these will be readily visible with the head thrown back and the neck fully extended (see Fig 2).

Group 2 persons with visible goitres. Persons with goitres which are easily visible with the head in normal position but which are smaller than those in Group 3 (see Fig 3). Palpation may be helpful in determining the mass of the gland, but is not needed for diagnosis.

Group 3 persons with very large goitres The goitres of persons in this category can be recognized at a considerable distance (see Fig. 4) They are grossly disfiguring and may be of such size as to cause mechanical difficulties with respiration and in the wearing of clothes

Organization of Survey

It has been found by experience that surveys for endemic goitre can be carried out most rapidly if blank forms are prepared to contain the necessary data on each individual examined. The name, age, sex, locality and years of residence in that locality are generally included, with a space for indicating previous residence when applicable. The date should always be indicated, and it is frequently helpful to have a place for the initials of the examiner when several persons are doing the survey.

It is essential to record certain pertinent information on each locality or population. This will include the size and type of locality, its altitude and perhaps its water-supply. When a school is examined, note should be [illegible] whether it is public or private and urban or rural. In localities [illegible] be of interest to [illegible] due to differences in the response to environmental influences. In this case, an indication of the race must be recorded on each individual form. In general, studies have

not indicated genetic factors to be important in influencing the prevalence of endemic goitre.

The numbers 0, 1, 2 and 3 should appear widely spaced, together with the letter " A " The number corresponding to the size of the thyroid gland encountered can then be conveniently circled The " A " can also be circled whenever nodules or adenomas are encountered An example of such a form appears in Annex 1 (see page 382).

These forms need not be large or use good quality paper and are just as useful if mimeographed or reproduced by some other process as if printed When examinations are being carried out in schools, it is more convenient to leave sufficient forms with the teachers at the school, to be filled in as far as possible on the day prior to the examination Usually a few words of instruction to the teachers collectively or individually will be sufficient Even when it is not possible to leave the forms with the teacher in advance, they can be distributed to each teacher prior to the examination and completed in a relatively short time. The teacher of older children can usually explain what is required in each space, so that the children can fill up their own forms The older children may then be asked to help the teachers of the lower grades to complete the necessary information on the forms.

In examinations in schools the children should be lined up by grades in front of the examiner with the data forms in their hands In the absence of another assistant, a teacher should be asked to act as recorder As each child steps forward, he should hand his paper to the recorder. The examining physician has only to call out the number indicating the size of the gland and indicate those cases in which the "A" is also be to circled In this manner an experienced person under ideal conditions can easily examine 150 to 200 children per hour This technique can be adapted to other institutional groups, such as orphanages, factories, nurseries, large farms, migratory labourers and refugee camps In general, the preparations will require as much time as the actual examinations

In many situations, especially when there is no expectation of returning to examine the same persons, the recording of the name takes unnecessary additional time In general, when the form has to be filled in at the time of examination, the data recorded can be limited to age, sex and locality Previous residence needs to be recorded only when there are a significant number of persons who have recently come to the area where the examination is being carried out.

In certain institutional situations it has been found to be more convenient to have the necessary data for many people listed in tabular form in advance on a single sheet and have them called for examination in the order in which their names appear. For certain types of population studies, it is also possible, with the co-operation of the local authorities, to assemble a sufficiently large and representative group by publicizing in advance that free examinations will be held in some convenient public place.

Selection of Sample[a]

The sample to be examined in endemic goitre surveys should represent, as far as possible, the different population groups and geographical localities of the country. For practical purposes, it is not necessary to attempt to determine the prevalence of goitre in a region or country with a high degree of accuracy. Ordinarily, if the figures presented to the health officials are not in error by more than 25%, they can serve as an adequate basis for action For example, iodization of salt is indicated when an endemic goitre rate of 10% is obtained, even though the true rate may be anywhere between 7.5% and 12.5%. The higher the rate, the larger the absolute error when only 25% accuracy is attained, but also the less important this becomes from a practical point of view. A reported rate of 20% which represents a true rate anywhere between 15% and 25% is just as useful for practical purposes as one which has included the examination of so many persons that the true value is between 18% and 22%.

In planning the survey one of the major requirements is to ensure that the areas to be studied constitute a random sample of similar localities within a geographical area Geographical characteristics, agricultural patterns, water-supplies, racial distribution, economic status and even dietary practices, when known, should all be taken into consideration in selecting localities

Care must be taken to treat urban areas and larger towns and cities as different groups, even though they are within the same region, since there have been cases reported where the capital of a department or province had very little goitre while the prevalence in surrounding small towns was quite high. Within urban areas the higher economic groups, with their more varied food habits, are likely to have a relatively low prevalence compared with the inhabitants of poorer districts in the same town.

The number of persons within a region to be included in the survey varies according to the homogeneity of the area and the amount of goitre found. It has been suggested that approximately 1% of the population of a country or of a large geographical area within a country should be examined. In the case of densely populated areas, this may result in the examination of far more people than is necessary for practical purposes. On the other hand, in thinly populated districts in which the prevalence is relatively low, this size of sample may be entirely inadequate as a basis for recommendations to health authorities.

The degree of accuracy obtained from the sample from any relatively homogeneous area or group depends on the number of goitre cases encountered as well as on the number of persons examined. This is shown

[a] The authors are greatly indebted to Dr Oudh B. Tandon, Chief of the Division of Statistics of INCAP, for many of the concepts expressed in this section.

in the table below, where it can be seen that the examination of 96 persons is sufficient to give an accuracy of 25% when the goitre rate is 40%, and 150 persons when it is 20%, but 1216 persons must be examined to obtain this degree of accuracy when the goitre rate is only 5%. Thus, the table can be used both to help determine the size of the sample required and to estimate the degree of accuracy achieved for each area when the survey is completed. *It should be noted, however, that the figures in this table* apply only to data derived from a relatively homogeneous group or area.

RELATIONSHIP OF THE MAXIMUM LIKELY ERROR TO THE NUMBER OF PERSONS EXAMINED AND THE GOITRE RATE ENCOUNTERED

Percentage with goitre	Maximum likely error				
	10%	20%	25%	30%	40%
5	7600	1900	1216	855	485
10	3600	900	576	405	225
20	1600	400	256	180	100
30	932	233	150	105	58
40	600	150	96	68	38
50	400	100	64	45	25

In actual practice it will generally be convenient in surveys of schoolchildren to examine all the children in attendance at each school visited. A properly planned survey will usually result automatically in the examination of sufficient persons for the error involved in the estimate of percentage *prevalence to be relatively small Occasionally, however,* the number of persons available for examination representing a given situation may be so small as to raise doubts as to the validity of the conclusions. In such cases, reference to the above table will be helpful

The foregoing discussion emphasizes the fact that taking a simple percentage of the total population or of the school population will not prove to be the most efficient way of selecting a sample. In densely populated and homogeneous areas, such as a capital city, the small fraction of 1% may suffice, whereas in other circumstances 2% or 3% of the group should be examined. The sample should include all numerically important segments of the population in the age-groups studied from both a geographical and an occupational point of view, but need include no more of each relatively homogeneous population unit than is required to reach a reasonably reliable conclusion.

If the survey is conducted to determine the need for a national iodization programme, it should be unnecessary to spend time and money examining

Selection of Sample[a]

The sample to be examined in endemic goitre surveys should represent, as far as possible, the different population groups and geographical localities of the country. For practical purposes, it is not necessary to attempt to determine the prevalence of goitre in a region or country with a high degree of accuracy. Ordinarily, if the figures presented to the health officials are not in error by more than 25%, they can serve as an adequate basis for action. For example, iodization of salt is indicated when an endemic goitre rate of 10% is obtained, even though the true rate may be anywhere between 7.5% and 12.5%. The higher the rate, the larger the absolute error when only 25% accuracy is attained, but also the less important this becomes from a practical point of view. A reported rate of 20% which represents a true rate anywhere between 15% and 25% is just as useful for practical purposes as one which has included the examination of so many persons that the true value is between 18% and 22%.

In planning the survey one of the major requirements is to ensure that the areas to be studied constitute a random sample of similar localities within a geographical area. Geographical characteristics, agricultural patterns, water-supplies, racial distribution, economic status and even dietary practices, when known, should all be taken into consideration in selecting localities.

Care must be taken to treat urban areas and larger towns and cities as different groups, even though they are within the same region, since there have been cases reported where the capital of a department or province had very little goitre while the prevalence in surrounding small towns was quite high Within urban areas the higher economic groups, with their more varied food habits, are likely to have a relatively low prevalence compared with the inhabitants of poorer districts in the same town.

The number of persons within a region to be included in the survey varies according to the homogeneity of the area and the amount of goitre found. It has been suggested that approximately 1% of the population of a country or of a large geographical area within a country should be examined. In the case of densely populated areas, this may result in the examination of far more people than is necessary for practical purposes On the other hand, in thinly populated districts in which the prevalence is relatively low, this size of sample may be entirely inadequate as a basis for recommendations to health authorities.

The degree of accuracy obtained from the sample from any relatively homogeneous area or group depends on the number of goitre cases encountered as well as on the number of persons examined. This is shown

---

[a] The authors are greatly indebted to Dr Oudh B. Tandon, *Chief of the Division of Statistics of INCAP*, for many of the concepts expressed in this section

than schoolchildren, they can be tabulated in the same way. Each goitre rate for an area should be based on the examination of a sufficient number of persons to have an accuracy of at least 25% according to the criteria of the table on page 379.

Where family surveys have been carried out or where adequate information has been obtained for all age-groups, it will be possible to obtain an over-all figure for the prevalence of endemic goitre in a large area or a country by means of the tabulation indicated in Form 3 (see Annex 4, page 383). In the same way that weighted percentages were obtained in Form 2, the over-all figure for an age-group can be adjusted according to the percentage of the total population which it represents The sum of the weighted percentages will then give the rate for the total population of a country However, this is not as useful as it might appear because iodization programmes should be based on the current need for iodine which is best indicated by the prevalence of goitre in children

Observations to supplement Endemic Goitre Surveys

Cretinism is presumed to be a complication of severe endemic goitre An effort should be made to learn of the existence of persons with cretinism in endemic areas and, if possible, verify the diagnosis by actual examination of each case reported Deaf-mutism and mental deficiency have been commonly mentioned as more prevalent in goitrous areas, but satisfactory confirmation of this assertion is lacking If it is possible to determine the frequency of these conditions in severely goitrous areas by house-to-house visiting or from information furnished by school authorities, valuable evidence may be obtained by comparing these findings with those of similar studies in areas relatively free from goitre

It is also important to note information which may help to explain differences in prevalence between nearby communities This will include water-supply, altitude, prevailing agricultural or industrial activities, economic level, proximity to the sea and, when available, prevailing dietary habits. Not infrequently, the difference between water supplied from a lake and that supplied from deep wells will determine whether a community has a high prevalence of goitre or none at all Dietary information which suggests the high consumption of a food known to be goitrogenic, such as cabbage, will be pertinent, as well as the occurrence of a deficiency such as that of vitamin A which has been reported to have a similar effect [3,4] On the other hand, a high consumption of sea-food will tend to reduce the frequency of goitre

Summary

The classification of a population sample by size of thyroid glands gives a good estimate of the severity of iodine deficiency in an area without

sparsely populated and difficult-to-reach areas, the inclusion of which would not alter significantly the final over-all goitre rate encountered or the need for prophylactic measures. For most purposes an accuracy of 25% will suffice, even though the requirement of random sampling, together with the convenience of examining all persons available at a given time and place, will usually result in a much higher degree of accuracy.

Tabulation and Presentation of Survey Data

The tabulation of the data obtained in endemic goitre surveys must proceed in several stages. It is usually convenient, first, to tabulate the information according to the type and severity of goitre in each age and sex group for the different localities or populations studied. A typical summary sheet for this purpose (Form 1) is shown in Annex 2 (see page 382). The ages have been selected to provide an approximate separation of pre-school children, primary-school children, adolescents and adults. While in theory these ages might vary with the age of puberty and with educational practices in a country, the intervals of 0 to 5, 6 to 12, 13 to 18, and 19 and over are recommended for the sake of uniformity.

Form 1 can also be used to group data pertaining to political units such as cities, counties, provinces and departments. Although males and females are usually tabulated separately, it is not a matter of practical importance in persons 12 years of age and under. It is not correct to use Form 1 to total the number of persons with different kinds of goitre unless the age-groups are proportionally represented. Usually it is sufficient to estimate the severity of goitre in a population from inspection of the data alone, without making a quantitative summation. When the prevalence of group 2 and 3 goitres is so high that it is desirable to present figures showing this, they should be tabulated separately for each age-group, using Form 2.

Form 2, which is shown in Annex 3 (see page 383), is designed primarily for combining data by age-groups for the various political divisions of a country. Since many surveys will collect data only from children, the use of the form for the 6-12 age-group is illustrated. Moreover, the usual survey obtains values for different areas which cannot be averaged because they represent varying percentages of the total population. However, when the population of an area is known (column 1), the percentage of the total population which it represents can be calculated (column 2). Each percentage figure for the prevalence of goitre in an area (column 3) can then be multiplied by this percentage to determine the amount (column 5) which it should contribute to the total percentage.

When these figures are added, the estimated goitre rate for all persons in the age-group tabulated is obtained, as shown in the lower right-hand corner of Form 2. When sufficient data are available for age-groups other

Annex 3

FORM 2: SAMPLE TABULATION OF DATA FROM ONE AGE-GROUP IN SEVERAL LOCALITIES

Department or Province	Population 6-12 years	Percentage of total population 6-12 years	Percentage with goitre	Weighted percentage *
Progreso	1 400 000	40	20	8 0
Unión	175 000	5	28	1 4
Yoro	770 000	22	18	4 0
Granada	525 000	15	35	5 2
Cartago	630 000	18	30	5 4
Over-all total	3 500 000	100		24 0 (total goitre rate)

* Obtained by multiplying the figures in columns 3 and 4 and dividing by 100

Annex 4

FORM 3: SAMPLE TABULATION OF DATA FROM ALL AGE-GROUPS IN AN AREA OR COUNTRY

Age-group (years)	Total population in age-group	Percentage of total population	Percentage with goitre	Weighted percentage *
0-5	200 000	10	5	0 5
6-12	200 000	10	28	2 8
13-18	300 000	15	30	4 5
19 and over	1 300 000	65	25	16 2
Over-all total	2 000 000	100		24 0 (total goitre rate)

* Obtained by multiplying the figures in columns 3 and 4 and dividing by 100

REFERENCES

1 Eggenberger, H (1928) In Hirsch, M , *Handbuch der inneren Sekretion*, Leipzig
2 Food and Agriculture Organization of the United Nations (1954) *Report of the Third Conference on Nutrition Problems in Latin America, Caracas, Venezuela, 19-28 October 1953*, Rome (FAO Nutrition Meetings Report Series, No 8)
3 Greer, M A (1950) *Physiol Rev*, **30**, 513
4 Haubold, H (1951) *Verh dtsch Ges inn Med*, **57**, 112
5 Scrimshaw, N S (1954) *Bol Ofic sanit panamer*, **34**, 277
6 Scrimshaw, N S et al (1953) *Lancet*, **2**, 166

the need for considering the functional status of the thyroid. Since the criteria for the diagnosis of goitre should be the determination of the degree of enlargement or the presence of adenomatous nodules and not its visibility, the use of the palpation method is recommended as the most accurate and reliable way of diagnosing the severity of the endemic goitre problem.

Annex 1

SAMPLE INDIVIDUAL FORM FOR ENDEMIC GOITRE SURVEY

Department Cocle

Locality : Santa Ana *Type of place:* Primary school

Years in locality: 12 *Former residence:*

Name Juan Pérez *Sex:* M *Age:* 12 *Race:* W

Thyroid·

0 <u>1</u> 2 3 A

Other observations: *Examiner:* RGB

Annex 2

FORM 1: SAMPLE TABULATION OF DATA FROM A LOCALITY

Place: Chepo *Political unit (Department, State, County or Province)*. Cartago *Date:* April 1962
Type of population: Primary school *Classification* Urban

Sex	Age-group (years)	Normal	D 1	D 2	D 3	A. 1	A. 2	A 3	Total exa-mined	Total positive	Per-centage positive
Male	0-5	—	—	—	—	—	—	—	0	—	—
"	6-12	77	55	10	2	15	1	0	160	83	52
"	13-18	2	2	3	0	1	0	0	8	6	**
"	19 and over	3	2	1	0	0	0	0	6*	3	**
Female	0-5	—	—	—	—	—	—	—	0	—	—
"	6-12	65	69	2	0	3	1	0	140	75	54
"	13-18	2	4	1	0	0	0	0	7	5	**
"	19 and over	1	3	0	0	1	0	0	5*	4	**

D = diffuse, A = adenomatous
* School-teachers
** *Percentage not given owing to the small number of people examined*

Annex 3

FORM 2: SAMPLE TABULATION OF DATA FROM ONE AGE-GROUP IN SEVERAL LOCALITIES

Department or Province	Population 6-12 years	Percentage of total population 6-12 years	Percentage with goitre	Weighted percentage *
Progreso	1 400 000	40	20	8.0
Unión	175 000	5	28	1.4
Yoro	770 000	22	18	4.0
Granada	525 000	15	35	5.2
Cartago	630 000	18	30	5.4
Over-all total	3 500 000	100		24.0 (total goitre rate)

* Obtained by multiplying the figures in columns 3 and 4 and dividing by 100

Annex 4

FORM 3: SAMPLE TABULATION OF DATA FROM ALL AGE-GROUPS IN AN AREA OR COUNTRY

Age-group (years)	Total population in age-group	Percentage of total population	Percentage with goitre	Weighted percentage *
0-5	200 000	10	5	0.5
6-12	200 000	10	28	2.8
13-18	300 000	15	30	4.5
19 and over	1 300 000	65	25	16.2
Over-all total	2 000 000	100		24.0 (total goitre rate)

* Obtained by multiplying the figures in columns 3 and 4 and dividing by 100

REFERENCES

1 Eggenberger, H (1928) In Hirsch, M, *Handbuch der inneren Sekretion*, Leipzig
2 Food and Agriculture Organization of the United Nations (1954) *Report of the Third Conference on Nutrition Problems in Latin America, Caracas, Venezuela, 19-28 October 1953*, Rome (FAO Nutrition Meetings Report Series, No 8)
3 Greer, M A (1950) *Physiol Rev*, **30**, 513
4 Haubold, H (1951) *Verh dtsch Ges inn Med*, **57**, 112
5 Scrimshaw, N S (1954) *Bol Ofic sanit panamer*, **34**, 277
6 Scrimshaw, N S et al (1953) *Lancet*, **2**, 166

THERAPY AND PROPHYLAXIS OF ENDEMIC GOITRE

J. MATOVINOVIĆ, M.D.* &
V. RAMALINGASWAMI, M D , D Phil **

Historical Summary

Iodine therapy

Iodine has been used in the treatment of goitre much longer than for its prevention The peoples of the Pacific coasts of China and South America are known to have been eating seaweed for the cure of goitre long before history came to be written [66] Numerous references to the treatment of goitre are found in Chinese medical writings According to Bircher,[7] the ashes of sea sponges (*Spongia usta*)—in vine, powder and pill form—were used by the Chinese in the treatment of goitre as far back as 1500 B C *Pen-Ts'ao Kang-Mu*, a Chinese herbal with a final edition in 1578, recommends all the medicinal algae for the treatment of goitre (see Hume [36]) The Greeks had the same experience and so, probably, did all the other ancient peoples living on the shores of the sea In the twelfth century, Ruggiero Frugardi (Roger of Salerno) recommended an Electruarium containing the ashes of sea sponges for the treatment of goitre, and this remedy has been used for centuries.[79]

A new era in the therapy of goitre began shortly after Courtois discovered iodine in 1811 in the seaweed *Fucus vesiculosus* while producing saltpetre for Napoleon's armies [20] Prout [72] first used iodine in the treatment of goitre in 1816. Prout states that, at his suggestion, Dr Eliotson of St Thomas's Hospital adopted this treatment in 1819 It was, however, Coindet (1774-1848) who did more than anyone else to lay the foundations of the treatment of goitre with iodine [16 18] On 25 July 1820, he demonstrated before the Swiss Society of Natural Sciences the first results of this treatment [16]

* Department of Internal Medicine, School of Medicine, University of Michigan, Ann Arbor, Michigan
** Research Professor of Pathology, All-India Institute of Medical Sciences. Formerly, Pathologist, Indian Council of Medical Research, New Delhi, India

In some cases the goitre regressed within a few weeks of the administration of iodine, in others it remained refractory. He noticed that some patients developed further enlargement of the goitre during treatment. He described iodism and was the first to draw attention to the development of hyperthyroidism during iodine medication—later called Jod-Basedow—and ascribe it to excessive dosage of iodine. Although he did not realize that his own prescriptions contained excessive quantities of iodine, he warned his readers to stop treatment forthwith when symptoms of hyperthyroidism appeared With characteristic foresight he seems to have anticipated the unhappy fate of his medicament and the damage to prestige it would suffer owing to ignorance, carelessness and prejudice, for he concluded: [18] "I cannot sufficiently emphasize the well-known axiom of Boerhaave, *at prudenter a prudente medico, si methodum nescis, abstine...* "

The pioneer work of Coindet was doomed to failure in the state of knowledge then existing The doses of iodine used were too large. According to Eggenberger [26] they amounted to 2500 to 5000 times the optimum Iodism was frequent The fear of iodine-induced hyperthyroidism or Jod-Basedow increased, and under the influence of Theodor Kocher reached its zenith This encouraged treatment with iodine to be restricted to short periods only, with the result that recurrence of goitre was common. No selection of cases for treatment was exercised and so disappointing results were frequent, especially in cases with nodular goitre. All these factors combined to lower the prestige of iodine, and iodine therapy fell into disrepute towards the close of the nineteenth century.

Baumann's discovery, in 1896, that iodine is the normal constituent of the thyroid gland provided the rallying-point for a revival of iodine treatment and prophylaxis of goitre,[4] and the opinion began to gain ground that small doses of iodine could be successfully administered. Finally, as a result of the fine efforts in the early part of the present century of Marine and Kimball,[48, 53] Hunziger,[37] Eggenberger [24] and Wagner-Jauregg,[86] iodine has again found a place in the treatment of goitre.

Iodine prophylaxis

The use of iodine in goitre prophylaxis was a logical consequence of Coindet's successful treatment of goitre with iodine Boussingault [8] was the first to suggest the use of iodized salt for the prevention of goitre He lived for many years in Colombia, and there he learnt about the experience of the local people regarding the therapeutic effect of the salt obtained from an abandoned mine in Guaca in the Department of Antioquia. In 1825 Boussingault analysed this salt and found that it contained large quantities of iodine. In 1833 he suggested the iodization of salt as a means of preventing goitre—a suggestion that was subsequently supported by J. L. Prevost (quoted by De Quervain [21]) and by A. Chatin (quoted by Eggenberger [21]) The first experiment in goitre prophylaxis ever known was carried

out in France, in the Departments of Bas-Rhin, Seine-Inférieure, and Haute-Savoie[21] Goitrous families received salt fortified with 0.1 to 0 5 g of potassium iodide per kg of salt. Schoolchildren with goitre received, daily, tablets or a solution containing 0 01 g of potassium iodide. Open bottles containing elemental iodine were placed in bedrooms In view of the high doses of iodide used in this programme, it is small wonder that toxic symptoms of iodism and Jod-Basedow were frequent and that, consequently, iodide prophylaxis was discredited and abandoned.

The true foundation of the iodine prophylaxis of endemic goitre was laid by Marine & Kimball[53 55] when they launched the first large-scale experiment in goitre prevention in Akron, Ohio, USA, in 1917. About 5000 girls, between 11 and 18 years of age, took part in this experiment. 2190 of them were given a daily dose of 0 2 g of sodium iodide in water for ten days in the spring and ten days in the autumn, making a total dose of 4 0 g over the year The remaining 2305 girls acted as controls The results are summarized in Table I. Two facts stand out from these data (a) in the group receiving sodium iodide, out of 908 girls with a normal thyroid prior to treatment, only 2, i e , 0 2%, developed goitre, whereas among the 1257 girls of the control group with previously normal thyroid, goitre appeared in 347, or 27 6%, (b) in the treated group, 773 out of 1282 girls with goitre, i e , 60 4%, showed a considerable decrease in the size of the thyroid, while in the control group spontaneous regression of the goitre

TABLE I RESULTS OF IODINE PROPHYLAXIS IN AKRON, OHIO, USA, FROM 1917-1919 *

Size of the thyroid	With iodine		Without iodine	
	No	%	No	%
Normal				
Unchanged	906	99 8	910	72.4
Increased	2	0 2	347	27 6
Slightly enlarged				
Unchanged	477	41 9	698	72 8
Increased	3	0.3	127	13 3
Decreased	659	57 8	134	13 9
Moderately enlarged				
Unchanged	29	20 3	57	64 0
Increased	—	—	21	23 6
Decreased	114	79 7	11	12 4
Total	2190	100 0	2305	100 0

* After Marine & Kimball[55] by kind permission of the editors of the *American Journal of the Medical Sciences*

occurred only in 145 out of 1048 girls, i e., 13.8%. Both the prophylactic and the therapeutic effects were thus impressive. Iodism was very rare (only 11 cases) in spite of the extremely large doses of iodine, and the symptoms disappeared within a few days of stopping the administration of sodium iodide.

Mass prophylaxis of goitre with iodized salt was first introduced on a community scale in Michigan in 1924 (Kimball [42]). Goitre surveys in schoolchildren and iodine analyses of the drinking-water were first carried out in 4 representatives counties, namely Houghton, Wexford, Midland and McComb, with the following results·

County	Iodine in drinking-water µg/litre	Goitre rate %
Houghton	0	64.4
Wexford	0 5	55 6
Midland	7 3	32.7
McComb	8 7	26 0

The average goitre rate among the 65 537 schoolchildren examined was 38.6%. Table salt containing 1 part in 5 000 of potassium iodide was then introduced and by 1929 the rate had fallen to 9%. The latest survey conducted by Brush & Altland [13] in 1951 on 53 785 schoolchildren in the same counties gave a goitre rate of only 1.4%. It was also reported that in 7 large hospitals in Michigan thyroidectomies accounted for only 1% of all operations in 1950 compared with 3 2% in 1939. No toxic symptoms of iodide prophylaxis were observed

Further historical details will be found in the chapter by Langer (page 9) and in the review by Kelly & Snedden of the world prevalence and geographical distribution of endemic goitre (page 27) The results of some more recent work are discussed in a later section of this chapter (page 404). Ample experience has now been gained to prove beyond doubt the value of iodine in the therapy and prophylaxis of endemic goitre and, at the same time, has revealed its limitations

Treatment with thyroid preparations

Compared with the numerous references to the use of seaweed, references in primitive medical writings to the use of thyroid preparations for the treatment of goitre are few.

According to James,[40] the ancient Chinese used to treat cretins with sheep's thyroid, and according to Schelenz [84] dried thyroid was suggested for the treatment of goitre in a Persian work, *Toahfi ul Moomineen*, completed in 1669 by Mir-Muhamed-Zeman-Tunkabuni This book was translated into Latin by Joseph de la Brosse in 1681. Richter, quoted by Schelenz,[84] claimed that the Persian edition appeared as early as the end of the fourteenth century. The prescription against goitre *Tryphere ad strumas* contained: *Strumarum colli arietis dessicatarum Dr. 5* It is not known

whether this prescription was used in Europe Following Murray's[60] successful treatment of myxoedema with a glycerol extract of thyroid gland, Sunderland, quoted by Angerer,[2] suggested in 1894 the use of thyroid for the treatment of goitre In the same year Reinhold[77] and Bruns,[10] who treated 350 cases of goitre with thyroid, published their results, which clearly showed that the administration of thyroid was of value in the treatment of goitre. The work which followed confirmed and extended their observations and provided a rationale for the treatment of goitre with thyroid preparations.[11, 12] However, despite many excellent publications—to mention but the work of Wagner-Jauregg[96] and Rienhoff[80]—this form of treatment of goitre has fallen into oblivion, probably because in the last fifty years the surgical therapy of goitre has made great progress, whereas the thyroid preparations have been discredited by improper application to various other diseases Recently, Greer & Astwood[34] admirably reviewed and reinvestigated the whole problem

Surgical treatment

In the first century A D, Celsus (quoted by Foote[29]) in *De re Medica*, Lib VII, Cap 13, recommended the treatment of cystic goitre by an incision made in the middle of the neck. The erudite Galen (A D 130-200), however, warned against surgical treatment (see Foote[29]) In A.D. 400, Susruta, the great exponent of Hindu medicine, prescribed five salts for the treatment of goitre and also advocated thyroidectomy The excision of goitre as a method of treatment did not make much headway, however, on account of the danger of excessive bleeding, which was first pointed out by Paulus Aeginita (A D 624-690) (see Foote[29]), and for many centuries surgical therapy was confined to attempts to shrink the goitre by means of inflammation To achieve this, red-hot seton-needles were passed through the goitre—an operation that resulted in copious bleeding, followed by dangerous suppuration[39] Until the beginning of the nineteenth century, thyroidectomy had probably been performed in no more than ten cases[1] The striking success of the surgical therapy of goitre today is inseparably linked with the name of Theodor Kocher (see Vogel[94]). Kocher performed 9000 thyroidectomies and effected striking improvements in surgical technique, from the incision in the skin to the closure and draining of the wound. Since these early days, the mortality from thyroidectomy has decreased progressively with improvements in technique. From 41 % in 1850[43] it fell to 12 8% in 1883,[43] 3 2% in 1910,[29] and 0 76% in 1941,[45] and today it is less than 0 2%[20] But the triumphs of goitre surgery were not unaccompanied by great disappointments. Post-operative complications such ae myxoedema, tetany and paralysis of the recurent laryngeal nerves wers not infrequent, but with better understanding of the anatomy and phsiology of the thyroid and parathyroid glands, these complications have now been largely overcome

Present-day Therapy of Endemic Goitre

Medical therapy

Iodine

Success in the treatment and prevention of endemic goitre—as of any other disease—depends upon a thorough knowledge of its etiology and the factors that promote its persistence and spread in the community. The etiology of endemic goitre has been one of the most intensely pursued lines of scientific inquiry in medicine There is now general acceptance of the opinion expressed by the Goitre Subcommittee of the Medical Research Council of Great Britain in 1944 that " the immediate cause of simple goitre is failure of the thyroid gland to obtain a supply of iodine sufficient to maintain its normal structure and function ".[31] At the same time, there is growing realization of the importance of factors other than iodine deficiency. A naturally occurring goitrogenic substance has been isolated from certain foods,[35] and recently a situation has been described by Clements in certain parts of Tasmania in which it appears that a goitrogenic substance with a capacity to inhibit the utilization of iodine by the thyroid may be responsible for the occurrence of endemic goitre there [15] It is clear that in such situations treatment with iodide may be of no avail, as has indeed been shown to be the case in Tasmania. The obvious thing to do in such cases is to remove, if possible, the source of goitrogen from the diet.

That treatment with iodine is indicated when the goitre has been shown to be due to absolute or relative deficiency of iodine is easily stated. In practice, however, the presence of iodine deficiency cannot be readily ascertained in individual cases unless a series of laboratory studies is made. *The simplest way is by a therapeutic test, but even then, the absence of* response does not prove that the goitre is not due to iodine deficiency. Indeed, according to the classical Marine cycle, [51] once a goitre, always a goitre: treatment with iodine may produce involution with deposition of colloid, but the gland does not revert completely to normal. It appears, however, that a diffuse hyperplastic gland can revert to normal and, in the early stage, it may become invisible after treatment with iodine. When the goitre has been of long standing and has passed through several Marine cycles, it tends to become large or nodular, or both The response to iodine in such cases will be variable, depending upon the extent of the hyperplastic zones Large cystic and degenerated goitres cannot be treated successfully with iodine and need surgical intervention

There is no definite opinion in the literature about the optimum therapeutic dose, the chemical compound of choice, or the duration of treatment with iodine The therapeutic dose should, in principle, be higher than the daily requirement, but in the present state of knowledge it is not possible to state how much higher it should be. One thing, however, is clear—namely, that large doses should not be administered, for then Jod-Basedow becomes

a real threat. Recently, Stanbury and his colleagues [89] reported a case of a woman with endemic goitre who developed thyrotoxicosis after the administration of 1500 μg of iodine per day. Owing to the avidity of the hyperplastic gland for iodine, the greater part of the iodine administered is taken up by the gland, a process which may last for several weeks [89] It is therefore quite unnecessary to use large doses in the treatment of endemic goitre We are of the opinion that the therapeutic dose need not be more than two or three times the daily requirement of iodine.

But what is the daily human requirement of iodine? Estimates of the minimum and optimum iodine requirements range widely, from 50 μg to 300 μg A great deal of work has been done in this connexion, but the validity of most of it has been subject to criticism "Taking the data for what they may be worth", Greenwald [32] calculates that the human requirement is less than 100 μg per day The Food and Nutrition Board of the National Research Council of the USA placed the optimum requirement at 150 to 300 μg for an adult, while the Committee on Nutrition of the British Medical Association recommended a daily minimum requirement of 100 μg for adults and suggested that a larger intake, 150 μg, might be advisable for children, adolescents and pregnant and nursing women [9] In the light of this knowledge we are of the opinion that the therapeutic dose need not be higher than 200 to 300 μg per day

The simplest prescription for iodine therapy is a solution of potassium iodide in water, as follows: potassium iodide, 0 03 g, distilled water, 20 0ml, 4 to 6 drops in a glass of water daily The most widely known preparation is Lugol's solution Lugol (quoted by Buchanan [14]) himself used three different prescriptions for potassium iodide with iodine The pharmacopoeias of most countries define Lugol's solution as iodine, 5 0 g; potassium iodide, 10 0 g; distilled water up to 100 0 ml This solution contains, in one drop, more than 300 μg of iodine and is therefore unsuitable for daily use Likewise, we are not in favour of using organic iodine preparations, since most of them contain large quantities of iodine Iodine compounds such as potassium iodide and iodate have been given in the form of tablets and sweets both for therapy and for prophylaxis with good results This form of treatment is particularly useful for schoolchildren and expectant and lactating mothers

Treatment has to be continuous and should be kept up until general prophylactic measures are established in the community. The therapeutic effect, if any, can usually be observed after 6-8 weeks of therapy If there is no response even after three months, then iodine should be replaced by thyroid preparations

Complications of iodine therapy are rare, but in the course of the treatment of goitre with iodine the following can occur: (*a*) iodism, (*b*) Jod-Basedow, (*c*) iodine thyroiditis, and (*d*) enlargement of the goitre with or without hypothyroidism

(*a*) *Iodism*. The allergic reaction to iodine can be either of an acute or of a chronic nature Acute iodism is manifested by angioneurotic symptoms, from urticaria to haemorrhagic exudates. Chronic iodism is more common than the acute form, the main symptoms being chronic rhinitis (like the common cold), enlargement of the salivary glands, and various acneiform exanthemas Earlier, iodism was observed fairly frequently among people over-sensitive to iodine, because the therapeutic dose was much larger. However, today this is not the case, the therapeutic dose of iodine being equal to, or only slightly larger than, the amount of iodine in the food of people in goitre-free areas

(*b*) *Jod-Basedow* The development of hyperthyroidism in the course of goitre therapy with iodine was described long ago by Coindet [17] and by Rilliet,[81] and has since been mentioned by many writers The name Jod-Basedow was first used by Kocher [44] in 1910. Many authors refused to recognize this condition, but, in 1951, Stanbury et al ,[89] while investigating the metabolism of iodine in goitrous people in the Province of Mendoza, Argentina, proved that Jod-Basedow can occur if the therapeutic dose of iodine is considerably larger than the daily requirement. However, the development of Jod-Basedow, like that of toxic adenoma, is inherent in the life history of the nodular goitre Hyperactive " hot nodules ", independent of the stimulating effect of thyrotropin, can develop in a goitre as a result of prolonged nutritional deficiency of iodine. It is these nodules that secrete almost all the hormone, the remaining thyroid tissue being practically inactive Given a larger supply of iodine they can produce excess of thyroid hormone, thus inducing Jod-Basedow Thus iodine does not cause but conditions the development of the disease. The distinction between the hyperactive nodule in the goitre of Jod-Basedow and the toxic adenoma of Plummer's disease lies only in the quantity of hyperactive tissue Many people with nodular goitre develop toxic adenoma in middle or old age, because in the course of time the hyperactive nodule increases in size and produces too much hormone, despite continued nutritional deficiency of iodine. This patho-physiological link between Jod-Basedow and toxic adenoma shows that the therapeutic dose of iodine must not be much larger than the daily requirement Hyperthyroidism developing during treatment with 200-300 μg of iodine suggests toxic adenoma, whereas hyperthyroidism developing on prolonged treatment with larger doses of iodine suggests Jod-Basedow. However, the differential diagnosis between Jod-Basedow and toxic adenoma can be very difficult; the only clinical difference lies in the fact that the symptoms of Jod-Basedow usually disappear spontaneously several weeks after the treatment with iodine has been discontinued Thus, hyperthyroidism occurring during the iodine therapy of goitre may be related to the administration of iodine, but is usually merely coincident with it; toxic adenoma and Graves' disease without exophthalmus are much more

common than Jod-Basedow. Consequently, the statistics on the occurrence of Jod-Basedow cannot be considered very reliable.

(*c*) *Iodine thyroiditis* Coindet,[17] and later many others, noticed that sometimes at the beginning of iodine therapy an enlargement of the goitre takes place which may be painful. According to Marine,[50] this complication can occur about the seventh day of therapy, if large doses of iodine are administered. However, after iodine therapy has been discontinued the goitre decreases spontaneously This complication can be explained on the assumption that the temporary hypersecretion of thyrotropic hormone causes the sudden formation of iodine-containing colloid in the follicles, with a decreased release of thyroid hormone into the blood-stream, perhaps due to the blocking effect of iodine This transitory harmless phenomenon is known as iodine thyroiditis [23, 50]

(*d*) *Enlargement of the goitre with or without hypothyroidism* The "iodine thyroiditis" described by earlier writers should be distinguished from the enlargement of the normal thyroid or goitre, with or without development of myxoedema, which occurs after the injection or oral administration of massives doses of iodine (50-500 mg or more per day) for the treatment of bronchial asthma,[5, 58] arteriosclerosis,[30, 46] goitre,[5, 38] and rheumatism,[58] or for diagnostic purposes [75] According to the studies of Wolff & Chaikoff,[102] Rawson et al ,[76] Morgans & Trotter,[58] Raben [74] and VanderLaan,[92] iodine-induced goitre arises because in some people (and in some animals) iodine in large doses inhibits the release of thyroid hormone into the blood-stream The shortage of thyroid hormone in the blood (sometimes down to the level of hypothyroidism), leads to a compensatory increase in the secretion of thyrotropin which produces enlargement of the thyroid Recently, Paris et al ,[67] in an excellent anatomical and biochemical study of iodine-induced goitre with hypothyroidism, have shown that. (i) the enlargement of the gland is due to diffuse hyperplasia of the thyroid parenchyma, (ii) iodine in large doses inhibits the formation of organic compounds of iodine in the thyroids of patients with this type of goitre, and, in contradistinction to the thyroids of normal individuals, the thyroids of such patients do not "escape" from this inhibitory effect when the administration of iodine is prolonged, (iii) this inhibitory effect of iodine occurs in these patients with smaller doses of iodine than in normal individuals, (iv) inhibition of the uptake of ^{131}I in the thyroid of these patients by small doses of iodine is more pronounced than in other individuals and is comparable with the effect of similar doses of iodine on the thyroid uptake of ^{131}I in patients with Graves' disease; (v) shortly after stopping iodine administration, the uptake of ^{131}I increases to a high level, but the formation of thyroid hormone is delayed for some time until the concentration of inorganic iodine in the serum returns to a normal level. This type of goitre disappears spontaneously after the admi-

nistration of iodine has been discontinued and the concentration of iodine in the blood has decreased.

All the above complications of the iodine therapy of goitre are very infrequent. Neither iodism nor iodine thyroiditis can occur with the dosage recommended here. Should either develop during the treatment of goitre with such doses of iodine, it can almost always be traced to an additional intake of iodine from some other source, such as a drug, mineral water, or cosmetic preparation. Cases of Jod-Basedow, too, are extremely rare Among more than 1000 adults, most of them with large nodular goitres, who received large doses of iodine (5-15 mg per day) under careful and frequent control, only one patient developed iodine thyroiditis, and one Jod-Basedow (J. Matovinović & N. Kovačić, unpublished data)

Thyroid preparations

Treatment with thyroid preparations is indicated in cases of endemic goitre since the gland becomes enlarged whenever it is unable to produce the necessary amount of thyroid hormone and is consequently under stimulation by the thyrotropic hormone of the anterior pituitary. By giving thyroid to meet the homeostatic needs of the organism, the secretion of thyrotropic hormone is decreased and involution of the hyperplastic tissue of the thyroid takes place. The therapeutic effect is more rapid with thyroid than with iodine. In the majority of cases of endemic goitre due to absolute or relative iodine deficiency, treatment with iodine alone is adequate This is especially true for children and adolescents Thyroid is indicated for adults with large goitres of the diffuse or, more frequently, of the nodular type containing, in addition to hyperplastic and macrofollicular parenchyma, degenerated, haemorrhagic, cystic and fibrotic tissue Thyroid is also indicated in cases of simple sporadic goitre, whether due to an innate defect in iodine metabolism, excessive intake of goitrogenic substances, or an unknown cause It is well known that the results of treatment of sporadic goitre with iodine are often disappointing. Treatment with thyroid becomes imperative if either endemic or sporadic goitre is associated with manifestations of hypothyroidism It is particularly indicated in newborn babies with goitre, since iodine is rather slow in its action and may occasionally induce temporary enlargement of the goitre, thus aggravating the pressure symptoms. Thyroid may be used with advantage to treat pregnant women with goitre. The tendency of the normal or goitrous thyroid gland to enlarge during pregnancy has been known for a very long time. Increase in the uptake of ^{131}I during pregnancy with euthyroidism has also been noted [48] Man et al [47] found that *the protein-bound iodine* (PBI) *in the serum* is higher on the average during pregnancy than either before or after, that its increase occurs earlier than the increase in the basal metabolic rate (BMR), and that miscarriages are commonest in women with a PBI level below 6 0 µg per

100 ml. Dowling et al [22] have shown that the heightened activity of the thyroid gland and the raised serum level of PBI during pregnancy are related to the increase in thyroxine-binding protein which is probably induced by the high oestrogen concentration in the blood Finally, some 50 years ago, Wagner-Jauregg [96] observed that when thyroid was administered during pregnancy to a goitrous woman who had previously given birth to four cretins in four successive deliveries her goitre diminished in size and a healthy baby with a normal thyroid was born

As there is a great deal of individual variation in response to thyroid extracts, the dose has to be adjusted to suit the individual. Apart from this, the minimum effective dose is dependent upon the amount of thyroid hormone that the gland is actually producing, however insufficient that may be. Greer & Astwood [34] effected complete cures of goitre with as small a dose as 0 65 mg of USP (United States Pharmacopoeia) thyroid in three out of a series of 50 cases. According to Means,[57] 100 mg of dried thyroid conforming to USP requirements (with a total organic iodine concentration of 0 22%) is the average substitutional dose of thyroid in fully developed myxoedema, and this may be taken to represent the amount required to meet the normal needs of the body The therapeutic dose has to be somewhat higher than this We suggest that treatment be commenced with 50 mg per day, the amount being gradually increased by weekly increments up to a maximum of 300 mg per day That this amount should be quite adequate in an average case of goitre is evidenced by the experiments of Werner et al [95] who showed that 70-75 mg of triiodothyronine daily (equivalent to 120 mg of thyroid) for 8 days will reduce the 24-hour uptake of ^{131}I by the thyroid from 35% to 11%

Diffuse hyperplastic goitres respond more readily and completely to thyroid than do nodular goitres In the series of 50 goitrous cases treated by Greer & Astwood,[34] 87% of diffuse goitres, 67% of multiple nodular goitres, and 67% of single nodular goitres decreased in size after treatment with thyroid The corresponding figures for the complete disappearance of the goitres in this series were 44%, 33% and 39%, respectively

Patients must be kept under observation during treatment A watch must be kept on the pulse rate, on the size of the thyroid gland and, if possible, on the BMR, blood cholesterol, and serum PBI The therapy should be discontinued for 14 days if toxic symptoms develop (thyrotoxicosis factitia) and thereafter resumed with a dose 25-50 mg smaller In general, treatment should be continued until the goitre diminishes in size In people with a normal thyroid who come into an area of severe endemic goitre, it takes three or four months for the goitre to develop To bring about a decrease in goitre size, the same or twice as long a period of treatment is necessary In about 50% of people, the withdrawal of thyroid therapy results in a recurrence of the goitres after about the same period of time In areas of endemic goitre due to iodine deficiency, regular thera-

nistration of iodine has been discontinued and the concentration of iodine in the blood has decreased.

All the above complications of the iodine therapy of goitre are very infrequent. Neither iodism nor iodine thyroiditis can occur with the dosage recommended here. Should either develop during the treatment of goitre with such doses of iodine, it can almost always be traced to an additional intake of iodine from some other source, such as a drug, mineral water, or cosmetic preparation. Cases of Jod-Basedow, too, are extremely rare. Among more than 1000 adults, most of them with large nodular goitres, who received large doses of iodine (5-15 mg per day) under careful and frequent control, only one patient developed iodine thyroiditis, and one Jod-Basedow (J. Matovinović & N. Kovačić, unpublished data).

Thyroid preparations

Treatment with thyroid preparations is indicated in cases of endemic goitre since the gland becomes enlarged whenever it is unable to produce the necessary amount of thyroid hormone and is consequently under stimulation by the thyrotropic hormone of the anterior pituitary. By giving thyroid to meet the homeostatic needs of the organism, the secretion of thyrotropic hormone is decreased and involution of the hyperplastic tissue of the thyroid takes place. The therapeutic effect is more rapid with thyroid than with iodine. In the majority of cases of endemic goitre due to absolute or relative iodine deficiency, treatment with iodine alone is adequate. This is especially true for children and adolescents. Thyroid is indicated for adults with large goitres of the diffuse or, more frequently, of the nodular type containing, in addition to hyperplastic and macrofollicular parenchyma, degenerated, haemorrhagic, cystic and fibrotic tissue. Thyroid is also indicated in cases of simple sporadic goitre, whether due to an innate defect in iodine metabolism, excessive intake of goitrogenic substances, or an unknown cause. It is well known that the results of treatment of sporadic goitre with iodine are often disappointing. Treatment with thyroid becomes imperative if either endemic or sporadic goitre is associated with manifestations of hypothyroidism. It is particularly indicated in newborn babies with goitre, since iodine is rather slow in its action and may occasionally induce temporary enlargement of the goitre, thus aggravating the pressure symptoms. Thyroid may be used with advantage to treat pregnant women with goitre. The tendency of the normal or goitrous thyroid gland to enlarge during pregnancy has been known for a very long time. Increase in the uptake of ^{131}I during pregnancy with euthyroidism has also been noted.[68] Man et al.[47] found that the protein-bound iodine (PBI) in the serum is higher on the average during pregnancy than either before or after, that its increase occurs earlier than the increase in the basal metabolic rate (BMR), and that miscarriages are commonest in women with a PBI level below 6.0 μg per

100 ml. Dowling et al.[22] have shown that the heightened activity of the thyroid gland and the raised serum level of PBI during pregnancy are related to the increase in thyroxine-binding protein which is probably induced by the high oestrogen concentration in the blood. Finally, some 50 years ago, Wagner-Jauregg[96] observed that when thyroid was administered during pregnancy to a goitrous woman who had previously given birth to four cretins in four successive deliveries her goitre diminished in size and a healthy baby with a normal thyroid was born.

As there is a great deal of individual variation in response to thyroid extracts, the dose has to be adjusted to suit the individual. Apart from this, the minimum effective dose is dependent upon the amount of thyroid hormone that the gland is actually producing, however insufficient that may be Greer & Astwood[31] effected complete cures of goitre with as small a dose as 0 65 mg of USP (United States Pharmacopoeia) thyroid in three out of a series of 50 cases According to Means,[57] 100 mg of dried thyroid conforming to USP requirements (with a total organic iodine concentration of 0 22%) is the average substitutional dose of thyroid in fully developed myxoedema, and this may be taken to represent the amount required to meet the normal needs of the body. The therapeutic dose has to be somewhat higher than this We suggest that treatment be commenced with 50 mg per day, the amount being gradually increased by weekly increments up to a maximum of 300 mg per day That this amount should be quite adequate in an average case of goitre is evidenced by the experiments of Werner et al[95] who showed that 70-75 mg of triiodothyronine daily (equivalent to 120 mg of thyroid) for 8 days will reduce the 24-hour uptake of ^{131}I by the thyroid from 35% to 11%

Diffuse hyperplastic goitres respond more readily and completely to thyroid than do nodular goitres In the series of 50 goitrous cases treated by Greer & Astwood,[31] 87% of diffuse goitres, 67% of multiple nodular goitres, and 67% of single nodular goitres decreased in size after treatment with thyroid The corresponding figures for the complete disappearance of the goitres in this series were 44%, 33% and 39%, respectively

Patients must be kept under observation during treatment A watch must be kept on the pulse rate, on the size of the thyroid gland and, if possible, on the BMR, blood cholesterol, and serum PBI The therapy should be discontinued for 14 days if toxic symptoms develop (thyrotoxicosis factitia) and thereafter resumed with a dose 25-50 mg smaller In general, treatment should be continued until the goitre diminishes in size In people with a normal thyroid who come into an area of severe endemic goitre, it takes three or four months for the goitre to develop To bring about a decrease in goitre size, the same or twice as long a period of treatment is necessary. In about 50% of people, the withdrawal of thyroid therapy results in a recurrence of the goitres after about the same period of time In areas of endemic goitre due to iodine deficiency, regular thera-

peutic doses of iodine should be administered after thyroid therapy has been discontinued, until general prophylactic measures are established In some patients, however, goitre may develop again despite iodine therapy, particularly in women of child-bearing age and people with a biologically inferior thyroid. Relapse is also very common in patients with sporadic goitre. In such cases, thyroid therapy should be continued for the rest of the patient's life. Thyroid administration must also be continued as a substitution therapy in cases of hypothyroidism, with such individual adjustment of dosage as is required The development of hypothyroidism (Farquharson's phenomenon [27]) and hyperthyroidism in patients with simple goitre after withdrawal of thyroid treatment has been described in the literature, but such complications are very rare. Farquharson's phenomenon is due to temporary but prolonged inhibition of the secretion of thyrotropin after the exogenous thryoid hormone has been used up [33] Similarly, hyperthyroidism after withdrawal of thyroid therapy is due to the *rebound hypersecretion of thyrotropin*, followed by hyperactivity of the thyroid due to the lag in the readjustment of thyrotropin secretion [33]

Some patients suffer from nausea and vomiting after taking thyroid In such cases, either thyroxine or triiodothyronine can be used instead of desiccated thyroid. According to Werner,[99] 0 12 g of USP thyroid is approximately as effective as 300 μg of L-thyroxine sodium or 75 μg of L-triiodothyronine orally, and represents the average maintenance dose for treatment of myxoedema. The maximum dose for the therapy of myxoedema with L-thyroxine sodium is about 500 μg and with L-triiodothyronine about 125 μg per day.[99] These doses should be sufficient for the therapy of goitre too Zondek & Leszynsky [105] gave 960 and 920 μg of triiodothyronine to two patients with multiple nodular goitre and myxoedema over periods of 9 and 8 days, respectively. As a result of this treatment, the myxoedema disappeared, the goitre diminished in size, and all but one of the nodules regressed.

Surgical treatment

Surgical therapy is indicated in goitre: (*a*) when there are signs of compression; (*b*) when thyrotoxicosis supervenes on a nodular goitre; (*c*) when there is malignant transformation of the goitre; and (*d*) for cosmetic reasons. The signs of compression depend upon the part which is being compressed There may be compression of the larynx and trachea, leading to dislocation of these organs with dyspnoea, cough, stridor and hoarseness. In children and adolescents, the trachea is relatively soft and narrow, and even a small colloid goitre can induce signs of compression. There may be compression of the blood vessels—the internal jugular and subclavian veins and, in the case of right-sided substernal goitre, the superior vena cava as well In such cases, there will be dilatation of the

subcutaneous veins, cyanosis and oedema of the face, neck or extremities, and a feeling of congestion in the head upon bending Dysphagia develops when there is compression of the oesophagus, but this is rare. The goitre may press on the adjoining nerves—on the recurrent laryngeal nerves producing a low, husky voice; on the cervical sympathetic producing Horner's syndrome, or on the vagus (this is extremely rare) producing paroxysmal bradycardia and syncope The cervical and brachial nerve plexuses may be compressed, leading to occipital headaches, pain in the right shoulder, paraesthesia and weakness in the right arm, etc.

In endemic goitre areas, hyperthyroidism (toxic adenoma) in patients with pre-existent goitre is said to be common and to account for about 20% of all patients with hyperthyroidism.[56] All agree that surgery is the best treatment for toxic adenoma

Opinions differ with regard to the importance of nutritional iodine deficiency in the development of cancer of the thyroid, but it is generally accepted that surgical therapy is indicated whenever cancer of the goitre is suspected By surgical measures it is usually possible to alleviate all the complications of goitre. Unfortunately, surgical therapy is often responsible for new complications, which are of great importance for the health, working capacity, and life of the patient. These include *(a)* temporary paralysis of the recurrent nerves in about 5% of cases and persistent paralysis in 1.3%;[78] *(b)* temporary hypoparathyroid tetany in about 0 94%, and persistent hypoparathyroid tetany in about 0.5%, of the patients;[78] *(c)* postoperative hypothyroidism (temporary and persistent) in about 9% of cases[87] The recurrent goitre is very frequent, surgical removal of such goitres accounting for about 5 9% of all thyroidectomies[78] It is therefore always necessary to try treatment with thyroid before undertaking thyroidectomy In a considerable number of patients the goitre will diminish after thyroid treatment, thereby making operation either unnecessary or at least much easier Therapy with iodine or thyroid is especially indicated after thyroidectomy, since the same factors which brought about the goitre continue to act, while a considerable part of the normal tissue as well as the exhausted and degenerated tissue has been removed by the operation

Other methods of treatment

Considering the fact that, as late as 1867, J Saint-Lager (quoted by Eggenberger[26]) counted 43 different theories to explain the etiology of endemic goitre, it is scarcely surprising that so many forms of treatment have been advocated in the past These will not be considered here except to make a brief reference to the more recent developments X-ray[83] and radium therapy[8] have been applied to endemic goitre, but no significant results have been obtained, and this approach does not fit in with the conception that goitre is a compensation for the shortage of thyroid hormone

The administration of the thyrotropic hormone has been advocated in selected patients with colloid goitres rich in iodine [101] and some successful results have been obtained.[59] We consider, however, that there is no justification for this form of treatment in endemic goitre, since in such patients the concentration of thyrotropin in the blood is probably already elevated. Furthermore, the therapeutic effect of thyrotropic hormone, if any, is limited to iodine-rich goitres which, in any case, would be in the process of undergoing spontaneous involution.

A decrease in the size of sporadic goitres, resistant to iodine treatment, has been reported following administration of bismuth salts (Villaverde [93]). It is difficult to evaluate this report, however, since the author did not have adequate controls.

The present methods of medical and surgical therapy of goitre represent a great advance in medicine, but they are intended for the treatment of individual patients. Since endemic goitre greatly affects the health and well-being of whole nations, however, modern treatment should be combined with general goitre prophylaxis. The importance of this principle has been admirably summed up by Marine. [49] "The old adage that one ounce of prevention is worth a pound of cure is outdone in the case of goitre, where one milligram of prevention is worth more than a thousand milligrams of cure."

Prophylaxis of Endemic Goitre

Principle of prevention

It has already been stated that successful prevention of any disease depends upon a thorough understanding of its etiology and epidemiology. It is now recognized that goitrogenic factors in food may be responsible for iodine-refractory endemic goitre (Clements [15]) and that excessive intake of calcium salts can be goitrogenic (Taylor [91]). But none of these advances has shaken the fundamental principle of the mass prophylaxis of endemic goitre, which is to increase the intake of iodine, within limits of safety, to ensure that it not only makes good the deficient intake but also, where possible, overcomes the effects of any goitrogenic factors present.

It is needless to emphasize that any large-scale programme of goitre prevention should be preceded by a study of the etiology of the disease and an assessment of the degree of iodine deficiency in that area. There may be situations where the intake of iodine *per se* is adequate, but where goitre is still prevalent because of other factors, for example, excessive hardness of drinking-water. In such cases, it may be possible to reduce the incidence of goitre by changing the water-supply from hard to soft water without increasing the intake of iodine. In undertaking such measures, however, the expense involved will be an important factor.

Medium for supplementary iodine

It is generally accepted that the most practicable method of providing supplementary iodine is the iodization of salt. Other methods have been tried from time to time, such as the iodization of water-supplies, the iodization of bread, and the periodical administration of iodide tablets and sweets for the protection of the vulnerable groups of the population. The iodization of water-supplies was practised extensively in the Netherlands before and during the Second World War, but it has now been abandoned as uneconomic, since only a small proportion of the water-supply—about 1% according to Olesen [65]—is used for drinking and cooking purposes. Moreover, it cannot be applied to areas that lack municipal water-supplies. In countries where bread is consumed as a staple foodstuff, the iodization of bread appears to be a satisfactory method. Introduced as a wartime measure in the Netherlands, it was found to be both economic and feasible (E. H. Hipsley, unpublished report, 1952). However, the consumption of bread varies greatly with individuals, age-groups and various strata of the population. Medicated tablets and sweets have been used extensively in goitre prophylaxis and have the advantage that they make it possible for a measured amount of iodine to be administered. This method is sound in principle, since iodine can be stored in the thyroid gland, and is indeed valuable as a temporary measure in periods of increased requirements, such as puberty, pregnancy and lactation. However, since the tablets are given at intervals and contain amounts of iodine far in excess of the daily requirements, there is a possibility, although remote, of the development of Jod-Basedow, as described by De Quervain [21] in a girl aged 9 years. Moreover, as a permanent measure for the greater part of the population the usefulness of such tablets would be dependent upon the efficiency of the distributing system and the co-operation of the people, both of which are difficult to ensure at all times. Iodized salt suffers from none of these disadvantages. Whether rural or urban communities are involved and irrespective of the dietary habits of the people, it is safe and reliable, and is the least expensive method of providing a continuous supply of iodine.

Level of iodization of salt

In deciding upon the level of ... [illegible]

of salt. It has already been stated that our knowledge of the iodine requirement is incomplete. The present method of expressing it in terms of body-weight and age leaves much to be desired. It will be readily agreed that the ideal method of expressing nutrient requirements would be in terms of bodily functions which depend specifically upon the particular nutrient

The administration of the thyrotropic hormone has been advocated in selected patients with colloid goitres rich in iodine [101] and some successful results have been obtained.[59] We consider, however, that there is no justification for this form of treatment in endemic goitre, since in such patients the concentration of thyrotropin in the blood is probably already elevated. Furthermore, the therapeutic effect of thyrotropic hormone, if any, is limited to iodine-rich goitres which, in any case, would be in the process of undergoing spontaneous involution.

A decrease in the size of sporadic goitres, resistant to iodine treatment, has been reported following administration of bismuth salts (Villaverde [93]) It is difficult to evaluate this report, however, since the author did not have adequate controls.

The present methods of medical and surgical therapy of goitre represent a great advance in medicine, but they are intended for the treatment of individual patients. Since endemic goitre greatly affects the health and well-being of whole nations, however, modern treatment should be combined with general goitre prophylaxis. The importance of this principle has been admirably summed up by Marine: [49] "The old adage that one ounce of prevention is worth a pound of cure is outdone in the case of goitre, where one milligram of prevention is worth more than a thousand milligrams of cure."

Prophylaxis of Endemic Goitre

Principle of prevention

It has already been stated that successful prevention of any disease depends upon a thorough understanding of its etiology and epidemiology. It is now recognized that goitrogenic factors in food may be responsible for iodine-refractory endemic goitre (Clements [15]) and that excessive intake of calcium salts can be goitrogenic (Taylor [91]) But none of these advances has shaken the fundamental principle of the mass prophylaxis of endemic goitre, which is to increase the intake of iodine, within limits of safety, to ensure that it not only makes good the deficient intake but also, where possible, overcomes the effects of any goitrogenic factors present.

It is needless to emphasize that any large-scale programme of goitre prevention should be preceded by a study of the etiology of the disease and an assessment of the degree of iodine deficiency in that area There may be situations where the intake of iodine *per se* is adequate, but where goitre is still prevalent because of other factors, for example, excessive hardness of drinking-water. In such cases, it may be possible to reduce the incidence of goitre by changing the water-supply from hard to soft water without increasing the intake of iodine. In undertaking such measures, however, the expense involved will be an important factor.

ference further recommended that where goitrogenic factors are shown to be important, the higher level of 1 in 10 000 should be adopted.

It would be unwise to recommend one level of iodization of salt for all areas. The level selected for each area must depend, in the ultimate analysis, upon a proper appraisal of the various factors mentioned earlier. Generally speaking, the authors are inclined to agree with the recommendation of the WHO Study-Group on Endemic Goitre,[103] since all available knowledge goes to show that the human requirement for iodine is probably less than 100 μg per day. In his James D. Bruce Memorial Lecture for 1954, Marine,[52] the pioneer of iodine prophylaxis, made the following statement: "Since the dangers of Jod-Basedow are serious in endemic goitre regions with a high incidence of advanced adenomatous goitre, it would seem advisable to use (as Switzerland has) a conservative iodide supplement (1:100 000) rather than greater concentrations." We would emphasize, however, that suitable adjustments of this level should be made according to the local conditions. Indeed, we believe that in the present state of knowledge it may be advisable to use different levels of iodization in different countries, and even within the same country, to assess their relative efficacy in controlling goitre.

Whenever general prophylaxis against goitre is attempted, provision must be made from the very beginning for assessment of its efficacy. The assessment may be made by doing goitre surveys at intervals, supplemented wherever possible by iodine metabolism studies, including studies with radioactive iodine. The pooled experience of countries using different levels of iodization will not only be of help in finding a rational level of iodization but will also throw light on the problem of iodine requirements.

Iodine compound for iodization of salt

In selecting the level of iodization of salt a factor of great importance is the purity of the salt. In large parts of the world where goitre is endemic the salt habitually used for domestic consumption is unrefined and has a relatively high moisture content. It is usually obtained either by solar evaporation of sea-water or from salt mines. Until very recently, the iodine compound used for fortification was either sodium or potassium iodide, more commonly the latter because it is less hygroscopic. It is now known that the impurities and moisture in unrefined salts facilitate the breakdown of iodides, with resultant loss of iodine. When using iodides for the fortification of unrefined salt, therefore, consideration must given to the amount of iodine that is likely to be lost during storage, and suitable adjustments must be made in the level of iodization. It has been shown that potassium iodate is the [illegible]

In the case of iodine, the appropriate physiological function would be the heat production of the body. It is of interest that as early as 1929 Orr & Leitch [66] estimated that the human requirement for iodine was of the order of about 20 to 40 μg per 1000 calories. Reference has already been made to the wide variations in the estimates of requirement made by different authors. In view of this, it is hardly surprising that the levels of iodization of salt adopted or recommended for adoption in various countries are widely divergent, as can be seen from the tabulation below.

Country	*Stipulated level of iodine compound in salt*
USA	1 in 10 000, as KI
Canada	1 in 10 000, as KI or NaI
New Zealand	1 in 20 000, as KI or NaI
Argentina	1 in 30 000, as KI
Mexico	1 in 66 000, as KI
England and Wales (all salt)	1 in 100 000, as KI
England and Wales (table salt)	1 in 40 000, as KI
Switzerland	1 in 100 000, as KI or NaI
Netherlands	1 in 100 000, as KI
Italy	1 in 100 000, as KI
Yugoslavia	1 in 100 000, as KI
Poland	1 in 200 000, as KI

It will be seen from the tabulation that the level adopted by the USA is 10-20 times as high as that adopted by some of the European countries. In selecting the higher levels the American authorities seem to have been guided by practical experience, based on the pioneer studies of Marine and Kimball, whereas in European countries the policy seems to have been based on the available knowledge about the requirements for iodine. From published accounts it would appear that both the higher and lower levels of iodization have been effective in controlling the endemic. These accounts, however, do not permit an assessment of the relative efficacy of each of the levels adopted

After a careful consideration of existing knowledge, the WHO Study-Group on Endemic Goitre,[103] which met in London in 1952, recommended that on the assumption that the daily consumption of salt is about 10 g and the salt is dry and pure, it would be advisable to iodize the salt with potassium iodide at a concentration of 1 part of iodide in 100 000 parts of salt. The Study-Group also stated that where the daily consumption of salt has been shown to be significantly different from the above figure of 10 g, suitable adjustments should be made in the concentration of the iodine compound added According to this recommendation, an individual is expected to receive about 76 μg of iodine daily from salt alone. The Third Conference on Nutrition Problems in Latin America,[28] held in Venezuela in 1953, recommended that the daily allowance of iodine should be of the order of 400 μg and concluded finally that the maximum level of iodization should be 1 part in 10 000 and the minimum 1 part in 20 000. The Con-

girls, is a sign of abnormality. It indicates that the thyroid gland is unable to produce the requisite amount of hormone at its normal size and undergoes hypertrophy and hyperplasia as an immediate compensatory reaction This compensatory mechanism, however, is not completely efficient [69, 71] In intelligence some goitrous children lag behind those with a normal thyroid. Therefore, the prophylaxis of "physiological" or "juvenile" goitre is indispensable, for, to quote Marine:[52] "The prevention of simple goitre means vastly more than preserving the normal outlines of the neck"

The decision to launch a mass control programme against goitre usually presents no difficulty in areas of high endemicity in which a substantial proportion of the population is affected and the goitre itself is large and nodular, producing marked disfiguration of the neck. If there is evidence

confronted with situations where the endemic is mild and goitre is largely confined to the adolescent age-groups. Goitres in adolescents are regarded by many as "physiological", and the question arises Where should one draw the line? In his survey of goitre prevalence among schoolchildren in England and Wales, Stocks [90] found a "residual" rate for thyroid enlargement of 1% for boys and 4% for girls aged 12 years, and considered these figures to be within normal limits Twenty years later, Murray and her colleagues [63] found a "residual" rate of 6% among English schoolchildren aged 11 to 15 years However, the occurrence of goitre in adolescents is not a normal phenomenon, for this type of goitre disappears as

iodine-deficient thyroid gland Querido et al [73] have shown that the 24-hour uptake of ^{131}I by the thyroid gland can be greatly increased (above 70%) and the iodine excretion in the urine be much reduced (below 25 μg/24 hours) even though no enlargement of the thyroid gland is detectable on palpation. Similarly, in a study on 53 well-nourished, healthy Indians from the Alto Ventuari region in the Amazon territory of Venezuela, Roche [82] found normal thyroids on palpation but an average 24-hour uptake of ^{131}I of 70 8% The increased thyroid uptake of ^{131}I in otherwise healthy people, especially when accompanied by a decreased excretion of iodine in the urine, justifies the postulation that iodine deficiency may exist and even persist in an area without development of goitre in some part of the population. When it is remembered that for every person with a visible enlargement of the thyroid there are at least two in whom the enlargement has not reached the clinical level, it will be observed that our suggested criterion for commencing general prophylaxis probably errs on the conservative side

TABLE II DIFFERENT TYPES OF SALT ENRICHMENT WITH IODINE*

Amount of iodine to be administered	Salt consumption per caput	Proportion of iodine to be added	Potassium iodate (mg/kg of salt)	Potassium iodide (mg/kg of salt)	Percentage of iodine
100 µg	5 g	1 . 50 000	33 7	22.14	0.002
	10 g	1 . 100 000	16 85	13 07	0 001
	15 g	1 150 000	11.23	8 71	0 00066
200 µg	5 g	1 . 25 000	67 40	52 28	0 004
	10 g	1 50 000	33 7	26.14	0 002
	15 g	1 . 75 000	22 47	17 43	0 00133
300 µg	5 g	1 16 600	101 1	78 42	0 006
	10 g	1 33 300	50 55	39 21	0 003
	15 g	1 : 50 000	33.7	26 14	0 002
400 µg	5 g	1 12 500	134 80	104 56	0 008
	10 g	1 25 000	67 40	52.28	0 004
	15 g	1 37 500	44 92	34 85	0 00266

Molecular weight of KIO_3 = 214
Atomic weight of I = 127
Conversion factor = $\frac{214}{127}$ = 1 685
1 685 mg of KIO_3 contain 1 mg of I

Molecular weight of KI = 166
Atomic weight of I = 127
Conversion factor = $\frac{166}{127}$ = 1 307
1 307 mg of KI contain 1 mg of I

* Reproduced by kind permission of Dr J M Bengoa

been shown to be effective in the prophylaxis of goitre.[86] It is important to remember that potassium iodate contains only 59.3% of iodine whereas potassium iodide contains 76.45%. Thus a salt containing 1 part of potassium iodide in 100 000 parts is equivalent in its iodine content to one containing 1 part of potassium iodate in 78 000 parts of salt. Table II, compiled by Dr J M Bengoa, gives the proportions of iodine to be mixed with the salt, based on the average salt intake.

Indications for general prophylaxis

It may be asked why endemic goitre should be prevented. Is it so significant from the public health point of view as to justify the effort and expense involved in its control? A detailed consideration of the scope of health problems directly attributable to endemic goitre is beyond the scope of this paper and will be found elsewhere.[a] It may be stated here, however, that in our opinion any clinically detectable enlargement of the thyroid, however mild and " silent " it may be and even if it is confined to adolescent

[a] See the chapter *Health significance of endemic goitre and related conditions* on page 235 of this monograph

TABLE III PROPHYLAXIS OF GOITRE OF THE NEWBORN IN BERNE, SWITZERLAND *

	Period of examination	Mean weight of thyroid (g)	Relative weight of thyroid (g/kg of body weight)
Without prophylaxis	1909-1914	9 99	2 43
	1915-1919	8 54	3 00
	1920-1924	8 89	3 12
With partial prophylaxis	1925-1929	6 99	2.31
	1930-1934	6 19	1 98
With general prophylaxis	1936-1938	3 74	1.28

* After Pradervand [71]

per kg of salt has thus proved sufficient to meet the needs of all the children and prophylaxis has been completely successful

Adults The influence of iodine prophylaxis on the mean weight of nodular goitres in men and women of various age-groups in the canton of

TABLE IV SIZE OF THE THYROID GLAND OF SCHOOLCHILDREN IN LAUSANNE, SWITZERLAND, FROM 1923-1937 *

Year of examination	Number of examined	Normal thyroid %	Thyroid enlarged on palpation %	Thick neck and goitre %
1923	383	42 3	51 5	6 2
1924	375	45 6	48 0	6 4
1925	310	45 2	49 0	5 8
1926	323	45 2	50 6	4 2
1927	317	44 2	49 9	5 9
1928	322	56 5	38 2	5 3
1929	508	81 9	16 7	1 4
1930	435	88 7	11 3	0
1931	270	90 0	10 0	0
1932	270	94 4	5 6	0
1933	251	96 0	4 0	0
1934	221	97 3	2 7	0
1935	237	98 7	1 3	0
1936	212	96 7	3 3	0
1937	285	99 3	0 7	0

* After Wespi [100] from data compiled by F M Messerli

Complications

Iodism and Jod-Basedow are remembered as complications of the earlier prophylaxis of goitre with large doses of iodine. The present-day prophylaxis of goitre is completely free from such problems. This has been proved by the experience in Switzerland[61] Our remarks on the development of iodism and Jod-Basedow in the course of goitre treatment are also relevant to goitre prophylaxis.

Recent Work on Goitre Prophylaxis

The recent work on the treatment and prophylaxis of endemic goitre is so abundant that most of it cannot even be mentioned in this chapter. The two studies described below will serve as examples of the wealth of experience now accumulating in all parts of the world

Switzerland

Impressive work on endemic goitre prevention has been accomplished in Switzerland under the supervision of the Swiss Goitre Commission. As early as July 1922, the Swiss Ministry of Public Health had recommended the introduction of iodized salt to all cantons. On the proposal of the Swiss Goitre Commission in 1923, both non-iodized and iodized salt were made available, the latter containing 5 mg of potassium iodide per kg.[25] The consumption of iodized salt gradually increased and in 1954 it amounted to 90% of the total salt consumption.[101] In several cantons iodized salt only is used, and in some this is obligatory. In 1951, the Swiss Goitre Commission accepted the proposal that the level of iodization should be increased to 10 mg of potassium iodide to 1 kg of salt, but so far only one canton has followed this suggestion.[101]

The results of this preventive measure have been excellent, and a considerable decrease in goitre prevalence has taken place in all age-groups [illegible] provides the best yardstick [illegible] yroid [illegible] and Anatomy in Berne, has determined the mean weight of the thyroid of the newborn over a period of 30 years From the results, shown in Table III, he has concluded that the introduction of prophylaxis with iodized salt containing 5 mg of potassium iodide per kg has considerably reduced the prevalence of goitre but has not prevented goitre completely.

Schoolchildren. Data for schoolchildren in Lausanne covering the period 1923-1937 have been compiled by Messerli and published by Wespi[100] (Table IV). It will be seen that the percentage of children with normal thyroids has risen from 42 3 to 99.3 and that, since 1930, none of the children has had a visible goitre. A level of iodization of 5 mg of potassium iodide

Central America

This study is described because it has yielded excellent information on the comparative effectiveness of potassium iodate and potassium iodide in the treatment and prevention of endemic goitre. In 1951-1952 Scrimshaw et al [86] of the Institute of Nutrition of Central America and Panama conducted a very well controlled study in El Salvador and Guatemala. Children, aged 5-14, in two rural schools in El Salvador and one school in Guatemala were surveyed. 811 children in El Salvador and 197 in Guatemala were examined by two examiners independently The frequency of goitre was found to be 34% and 57% respectively The children were divided into 3 practically equal groups One group was given placebo tablets containing dextrose, the other two groups were given tablets of similar appearance containing 6 5 mg of potassium iodide and 8 5 mg of potassium iodate respectively to supply each group with 5 0 mg of iodine This dose of iodine corresponds to a daily consumption of iodized salt at a level of 1 part per 10 000. All tablets were distributed once a week During the three treatment periods of 15 weeks and 20 weeks in El Salvador and 25 weeks in Guatemala no significant change in the goitre rate was observed in children receiving the placebos. In those receiving potassium iodide, the goitre rate was reduced by 40%, 33%, and 60%, whereas in those receiving potassium iodate it was reduced by 44%, 44%, and 69% during the three treatment periods.

Four weeks after the experiments were concluded, the protein-bound iodine in the children who had received placebos, potassium iodate and potassium iodide was 2 68 $\mu g \pm 1$ 20, 5 1 μg ± 1 19 and 4 97 $\mu g \pm 1$ 04 respectively

After the treatment had been discontinued for 16 weeks the prevalence of goitre in the Guatemala group returned to the original pre-treatment value No differences in the values of protein-bound iodine were found in children with or without goitre

The authors concluded that potassium iodate and potassium iodide in doses containing equal amounts of iodine are about equally effective in the treatment of endemic goitre. As potassium iodate is more stable than potassium iodide, the authors suggested that it should be given preference in the iodization of salt, especially in tropical and humid regions.

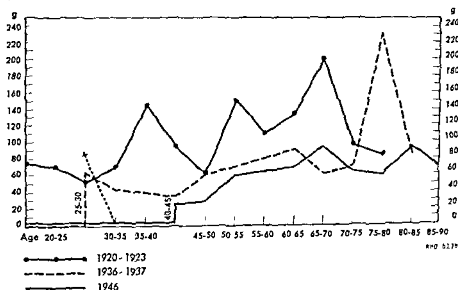
Conclusion

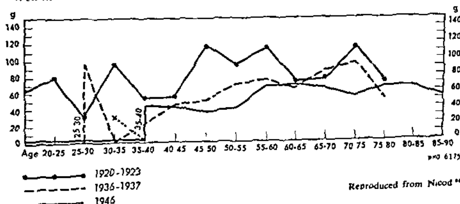
[illegible]

Endemic goitre is now regarded as a compensatory response to a variety of factors in an effort to maintain homeostasis, rather than as a static disease

Vaud is shown in the *accompanying* two graphs taken from the paper by Nicod.[61] A very rapid and substantial decrease in the average weight of the thyroid is evident in both sexes, with a somewhat more pronounced effect *in men* At the same time it will also be seen that whereas prior to 1924, nodular goitres were found in very young individuals, in 1936 no nodules were found in either men or women under 25 years of age By 1946, no cases of nodular goitre could be found in men under the age of 35 and only two exceptional cases in women under 40 years of age.

MEAN WEIGHT OF NODULAR THYROIDS IN ADULTS OF DIFFERENT AGE-GROUPS IN THE CANTON OF VAUD, SWITZERLAND, BEFORE AND AFTER THE INTRODUCTION OF IODIZED SALT





Reproduced from Nicod[61]

32 Greenwald, I (1955) *Amer J clin Nutr.*, **3**, 215
33 Greer, M. A. (1951) *New Engl J. Med*, **244**, 385
34 Greer, M. A. & Astwood, E B (1953) *J clin Endocr*, **13**, 1312
35 Greer, M A, Ettlinger, M. G. & Astwood, E B (1949) *J. clin Endocr*, **9**, 1069
36 Hume, E H. (1948) *Merck Rep*, **57**, 19
37 Hunziger, H (1915) *Der Kropf, eine Anpassung an jodarme Nahrung*, Bern
38. Hurxthal, L. M (1945) *Lahey Clin Bull*, **4**, 73
39 Hutchinson, C. A (1823) *Med-chir Trans*, **11**, 235
40 James, D W. (1955) *Lancet*, **1**, 1068
41. Kelly, F C (1953) *Bull Wld Hlth Org*, **9**, 217
42 Kimball, O P (1937) *J Amer med Ass*, **108**, 860
43. Kocher, T. (1883) *Arch klin Chir*, **29**, 254
44. Kocher, T. (1910) *Arch klin Chir*, **92**, 1166
45 Lahey, F H (1941) *Ann Surg*, **113**, 730
46 Lechelle, P. & Troisier, F (1950) *Bull Soc med Hôp Paris*, **66**, 960
47. Man, E B et al (1950) *J clin Invest.*, **30**, 137
48 Marine, D. (1914) *J. exp Med*, **19**, 70
49 Marine, D (1923) *Publ Hlth (Mich)*, **11**, 23
50 Marine, D (1927) *Medicine (Baltimore)*, **6**, 127
51. Marine, D (1928) *Certain features of the morphologic pathology of endemic goiter.* In· *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 68
52 Marine, D (1954) *Ann intern Med*, **41**, 875
53 Marine, D & Kimball, O P. (1920) *Arch intern Med*, **25**, 661
54 Marine, D & Kimball, O P (1921) *J Amer med Ass*, **77**, 1068
55 Marine, D & Kimball, O P (1922) *Amer J. med Sci*, **163**, 634
56. Matovinović, J, Kovačić, N & Prosenjak, M (1956) *Acta chir yugoslav*, **3**, No 4, p. 105
57. Means, J H (1948) *The thyroid and its diseases*, 2nd ed, Philadelphia, Lippincott, p 66
58 Morgans, M E & Trotter, W. R (1953) *Lancet*, **2**, 1335
59 Mortara, M (1935) *Minerva med (Torino)*, **2**, 287
60 Murray, G R (1891) *Brit med J*, **2**, 796
61 Murray, M M (1953) *Bull Wld Hlth Org.*, **9**, 211
62 Murray, M M & Pochin, E (1951) *J Physiol (Lond)*, **114**, 6
63 Murray, M M et al (1948) *Thyroid enlargement and other changes related to the mineral content of drinking water (with a note on goitre prophylaxis)*, London (Medical Research Council, Memorandum No 18)
64 Nicod, J L (1953) *Bull Wld Hlth Org*, **9**, 259
65 Olesen, R (1927) *Publ Hlth Rep (Wash)*, **42**, 1355
66 Orr, J O & Leitch, I (1929) *Spec Rep Ser med Res Coun (Lond)*, No 123, p 1
67 Paris, J, et al (1960) *J clin Endocr*, **20**, 57
68 Pochin, E E (1952) *Clin Sci*, **11**, 441
69. Podach, E F (1951) *Schweiz med Wschr*, **81**, 19
70 Pradervand, L (1940) *Endokrinologie*, **23**, 1
71. Prebeg, Z et al (1955) *Higijena*, **7**, 307
72 F [illegible]
73 C [illegible]
[illegible] 10), London, Churchill, p 124
74 Raben, M S J (1949) *Endocrinology*, **45**, 296
75 Raben, M S J (1953) *J clin Endocr*, **13**, 469
76 Rawson, R W. et al (1945) *J. clin Invest*, **24**, 869

entity, and iodine is recognized as an indispensable mineral nutrient rather than as a pharmacological agent in the treatment of goitre.

Effective and practicable measures for the control of goitre were known long before their rationale was understood. The situation today is completely reversed. Advances in our understanding of the etiology and pathogenesis of goitre have far outstripped the progress made in its control.

Marine's oft-quoted aphorism still bears repetition: "Simple goitre is the easiest of all known diseases to prevent... It may be excluded from the list of human diseases as soon as society determines to make the effort."

REFERENCES

1 Albert, E. (1890) *Lehrbuch der Chirurgie und Operationslehre*, 4th ed, Wien & Leipzig, vol 1, p 435
2 Angerer, O (1896) *Munch med Wschr.*, **43**, 69
3 Bartels, E. C & Higgins, G K. (1955) *Lahey Clin. Bull*, **9**, 48
4 Baumann, E (1896) *Z. physiol Chem*, **21**, 319
5 Bell, G O (1952) *Trans Amer Goiter Ass*, p 28
6 Bertiglia, B (1949) *Minerva med (Torino)*, **40**, 84
7. Bircher, E. (1922) *Schweiz. med. Wschr*, **52**, 713
8 Boussingault, J B (1833) *Ann Chim Phys*, **54**, 163
9 British Medical Association, Committee on Nutrition (1950) *Report of the Committee on Nutrition of the British Medical Association*, London
10 Bruns, P. (1894) *Beitr. klin. Chir*, **12**, 847
11 Bruns, P (1895) *Beitr. klin Chir.*, **13**, 303
12. Bruns, P (1896) *Beitr. klin. Chir*, **14**, 521
13 Brush, B E and Altland, J K (1952) *J. clin Endocr.*, **12**, 1380
14 Buchanan, J A (1928) *Ann med Hist.*, **10**, 202
15 Clements, F W (1955) *Med J. Aust*, **2**, 369
16 Coindet, J F (1820) *Bibl universelle Sci. Arts (Genève)*, **14**, 190
17 Coindet, J F. (1821) *Bibl. universelle Sci Arts (Genève)*, **16**, 140
18 Coindet, J F (1821) *Bibl. universelle Sci. Arts (Genève)*, **16**, 320
19. Colcock, B P (1955) *J Mich med Soc.*, **51**, No 1, p 76
20. Courtois, M. B (1813) *Ann. Chim (Paris)*, **88**, 304
21. De Quervain, F. (1922) *Schweiz med Wschr*, **52**, 857
22. Dowling, T J., et al. (1956) *J clin. Endocr.*, **16**, 1491
23. Edmunds, H. T (1955) *Brit. med. J*, **1**, 354
24. Eggenberger, H (1924) In. Hunziger, H., *Die Prophylaxe der grossen Schilddrüse*, Bern & Leipzig, p 284
25. Eggenberger, H. (1928) In Hirsch, M, *Handbuch der inneren Sekretion*, Leipzig, vol 3, p 809
26 Eggenberger, H, (1928) In. Hirsch, M, *Handbuch der inneren Sekretion*, Leipzig, vol 3, p. 836
27. Farquharson, R F. & Squires, A. H (1914) *Trans Ass. Amer Phys*, **56**, 87
28. Food and Agriculture Organization of the United Nations (1954) *Report of the Third Conference on Nutrition Problems in Latin America, Caracas, Venezuela, 19-28 October 1953*, Rome (FAO Nutrition Meetings Report Series, No 8)
29. [illegible] *J clin Endocr* **14** 1385
30. [illegible]
31. [illegible] ommittee (1944) *Lancet*, **1**, 107

IODIZED SALT

J. C. M HOLMAN, B Sc, F R.I C, M.I.Chem E.* &
William McCARTNEY, Ph D (Edin), F.R.I C.*

Since it is almost universally agreed that lack of iodine in food and drinking-water is the primary cause of simple endemic goitre, the obvious method of preventing the disease is to make good the deficiency. Prevention of goitre by administration of iodine is practised, therefore, chiefly to meet an absolute environmental deficiency of iodine, but it is equally effective where the disease results from factors which increase the normal iodine requirement Administration of iodine on a community scale, it should be noted, is undertaken *not* in order to alleviate existing goitre (although such administration may have useful effects in this direction also) but to limit and prevent the development of the disease

At various times and in various places, divers means have been adopted for mass administration of iodine In the Argentine,[63] the Netherlands,[60] the USSR[36] and the USA[52] water supplies have been iodized, and in Australia,[30] the Netherlands[17] and the USSR[37, 41] iodine has been administered in bread. On some occasions, chocolate, milk (or skim milk, dried), or tablets containing added iodine have been distributed to school-children and others And, quite recently, iodized oil, given by injection, has been suggested[44] for use in parts of New Guinea which are not easy of access, it having been claimed that a depot of 1 ml of the oil (iodine content 40%) would provide a continuous supply of iodine over a period of two years All these methods, however, suffer from disadvantages of one kind or another (iodization of a public supply of drinking-water, for example, is probably costly and wasteful although successful) and, as Kimball,[38] affirmed in 1938, " the most practical method yet devised " of adding " an exceedingly small amount of iodine to our food " is to consume iodized salt The only instances where this would not apply are in countries such as Thailand,[78] where common salt is not used in the households.

Some naturally occurring sources of sodium chloride, it is true, contain appreciable quantities of iodine but the proportion is seldom sufficiently

* Chilean Iodine Educational Bureau London

77 Reinhold, G (1894) *Munch. med. Wschr.*, 41, 613
78 Richard, M. (1951) *Schweiz med. Wschr.*, 81, 4
79. Richter, P. (1907) *Arch klin. Chir.*, 82, 951
80. Rienhoff, W. F. (1940) *Arch Surg (Chicago)*, 41, 481
81. Rilliet, M (1858-59) *Mém Acad Méd (Paris)*, 24, 23
82. Roche, M. (1959) *J. clin. Endocr.*, 19, 1440
83. Saitmacher, H (1953) *Strahlentherapie*, 90, 527
84. Schelenz, H (1910) *Arch Gesch Med.*, 4, 45
85. Schroeter, J. (1949) *Ciba Z.*, 10, 4358
86. Scrimshaw, N. S. et al. (1953) *Lancet*, 2, 166
87. Sloan, L. W & Frantz, V. K. (1955) *Sporadic non-toxic goiter*. In Werner, S. D., ed., *The thyroid*, New York, p. 353
88 Stacpoole, H H (1938) In: *Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter*, Washington, p 76
89 Stanbury, J. B et al (1954) *Endemic goiter. The adaptation of man to thyroid deficiency*, Cambridge, Mass., p 66
90. Stocks, P. (1928) *Quart. J Med.*, 21, 223
91. Taylor, S (1954) *J clin Endocr.*, 14, 1412
92 VanderLaan, W. P. (1955) *The thyroid* In: *Brookhaven Symposia in Biology No. 7*, New York, p. 30
93. Villaverde, M. (1949) *J clin. Endocr.*, 9, 462
94. Vogel, A. (1921) *Arch klin. Chir.*, 115, 5
95 Wagner-Jauregg, J. (1938) *Der offentliche Gesundheitsdienst. Mitteilungen des Ministeriums fur innere und kulturelle Angelegenheiten. Gesundheitswesen*, Sonderbeilage, p. 1
96. Wagner-Jauregg, J (1938) *Schweiz med Wschr.*, 68, 246
97 Wegelin, C. (1945) *Presse méd.*, 53, 514
98 Werner, S. C., et al (1955) *J. clin. Endocr.*, 15, 715
99. Werner, S. C., ed. (1955) *The thyroid*, New York, pp 740, 741
100 [illegible] 51, 490
101 [illegible] *h 30 Jahren*
102 [illegible]
103. [illegible] *Bull Wld Hlth Org.*, 9, 293
104 Youmans, J. B. (1950) *J. Amer med Ass.*, 143, 1252
105. Zondek, H & Leszynsky, H (1956) *Lancet*, 1, 77

followed, however, and the later recommendations by Grange[26] and Köstl[42] were likewise disregarded. In 1885, Franz Köstl, director and chief physician of the Royal and Imperial Lunatic Asylum in Prague, appealed to the Austrian Minister of the Interior to supply cheap sea-salt or iodized salt to the inhabitants of the regions of Styria where cretinism prevailed. He had found that out of a population of somewhat less than one million, nearly 6000 were cretins. It has been stated[11] that heavily iodized salt was used for a time in Austria, France and Italy about the middle of the 19th century, but it was not until the second decade of the 20th century that iodized salt was again recognized as the best medium for conveying additional dietary iodine to those in need of it. This was due almost entirely to the work of Marine and Kimball, who demonstrated the complete effectiveness of iodine as a goitre prophylactic and secured the introduction of iodized salt on a community scale in Michigan and Ohio[39, 40, 45-47]. Their work stimulated the re-introduction of iodized salt in Europe. On the recommendation of the Swiss Goitre Commission the use of iodized salt was commenced in various cantons in Switzerland during the years 1919-24[a]. In Italy measures were adopted in Valtellina in 1928. Somewhat later (1933-37) official sanction was given to the sale of iodized salt in Canada, New Zealand, Poland and the Netherlands, and other countries, notably the Central and South American republics, rapidly followed suit.

Extraction and Refining of Salt

Crude salt, usually containing considerable proportions of impurity, has been mined or extracted from brine either by solar evaporation or by evaporation over fire since a very early period in human history and such salt is still extracted and used as food today by primitive peoples and in the less developed countries. Moreover, in the industrially advanced countries, impure salt such as rock salt is mined and used without purification for other than nutritional purposes. However, in those countries which have important salt-manufacturing industries, the greater part of the salt used for domestic purposes is produced by the evaporation of brine, either in open pans or in multiple-effect evaporators[5] in which water is removed under reduced pressure to yield the so-called "vacuum" salt.

In the open-pan process, the brine is run into large, shallow, iron pans heated directly by solid fuel. The varieties of salt which separate differ considerably according to the temperature at which the separation of the crystals occurs—the higher the temperature, the finer the grain of the salt deposited. If it is desired to prepare lump salt, the material which crystal-

[a] It was believed in Switzerland that the iodization of salt could be accomplished extremely easily and, at first, the manufacturers simply poured iodide solution on to the salt, rubbed the moist portions with the hand and stirred for one or two minutes. Later, when the scale of the operation was greatly increased, they sprayed the solution on to the salt in a shaking machine or, alternatively, added potassium iodide to brine in the evaporating pans[33].

high to be of value for goitre prevention, although salt water is used prophylactically with success, after concentration, by the people of the Kelabit country in Sarawak.[21] As the sea is not rich in iodine, sea-salt is a very poor source of this element, however, by far the greater proportion of it being left behind in the mother-liquor during separation. Kimball's view has been accepted almost everywhere and iodized salt is now recognized by goitre authorities [81] as the most convenient and most effective vehicle for the administration of supplemental iodine If iodized salt were introduced everywhere for domestic use as a permanent measure in public health, simple goitre would become a disease of the past This fact is accepted today by the public health officials in the endemic goitrous areas of the world and the governments of many countries have taken or are initiating steps to ensure the provision of iodized salt in their territories. Already, 95% of the table salt retailed in New Zealand [12] is iodized and in the United States of America about 80% of the households use iodized salt.[77] It is reported that, in Ceylon, all edible salt is to be iodized.[10] Several Central and South American states (Argentina, Brazil, Colombia, the Dominican Republic, Ecuador, Peru) produce large quantities of iodized salt. More or less comprehensive measures of iodization have been undertaken in several European countries (especially those of eastern Europe), as well as in the USSR Australia, China, India, Rhodesia, and the Union of South Africa (In the United Kingdom, however, only 1%-2% of the table salt sold is iodized) In some cases, there are even salt substitutes on the market (e g., lithium chloride or potassium chloride) containing added iodide.

This degree of success in securing the adoption of measures for goitre prophylaxis has not been easily or rapidly achieved, however, and although it has rarely, if ever, been shown that the minute proportions of iodine in iodized salt have any adverse effects, either on the human organism or on foods which may be flavoured with the salt, opposition to its use has been expressed from time to time, particularly by the few who refuse to regard iodine deficiency as the primary cause of goitre. A recent letter from Greenwald [27] to the editor of the *Lancet* restating this point of view has been answered by Taylor.[73]

The general use of iodized salt in a goitrous area was first proposed by the distinguished French investigator Jean Baptiste Joseph Dieudonné Boussingault [9] (1801-1887) in the year 1831. Having observed a 'terrifying' number of sufferers from goitre in the cordilleras of New Grenada (now Colombia) where he was then working for an English mining firm, he conducted some researches into the cause of the disease and reached the following conclusions "I consider it certain that goitre would disappear from the Cordilleras if the authorities would take appropriate steps to have established in the capital of every canton where goitre is endemic, a depot of salt containing iodine whither every inhabitant could go to buy such salt as he required for his consumption." This advice was apparently not

produced by continuous vacuum-evaporation of brine is very easily and satisfactorily iodized by spraying with an aqueous solution of an iodine compound, and this method is adopted in the United Kingdom and other countries where important salt-manufacturing industries exist

"Vacuum" salt and any other fine salt may also be iodized by dry-mixing, batch processes, but these are expensive by comparison with the spraying technique and are not recommended for large-scale production.

Crystalline salt, made by heated open-pan evaporation of brine, can be iodized by regulated additions of small proportions of potassium iodide solutions to the brine. This can be undertaken effectively either in continuous processes or batch processes. A high degree of analytical control is required to achieve uniform iodization of the salt output For this reason, it is usually preferred to iodize open-pan salt by dry-mixing processes

In the Netherlands East Indies, blocks of salt are successfully iodized [18] by moistening with an aqueous solution of potassium iodide and sodium thiosulfate (1 ml per block) However, the coarse crystalline products obtained by crushing rock salt or by the solar evaporation of brine, which are the only types of salt available in many of the endemic goitre districts in the less developed areas of the world, cannot usually be iodized by the methods already mentioned Continuous, large-scale spraying techniques generally involve conveyor mechanisms and, as a rule, are designed to treat fine, free-flowing salt. Dry-mixing processes are likewise chiefly applicable to fine grades of salt and provide for the addition of non-caking and stabilizing compounds in addition to the iodizing agent. Moreover, the addition of solutions of iodine compounds to brine is convenient only when the evaporation proceeds at a predetermined rate, as in heated, open-pan processes Accordingly, all these techniques are, in general, unsuitable for the iodization of the coarse salts consumed by the inhabitants of the less developed countries, apart from being too expensive It has therefore been a major consideration of the World Health Organization, in its studies of the endemic goitre problem, to provide a suitable method In view of this extremely important matter, a new type of dry-mixing process was introduced a few years ago by the Chilean Iodine Educational Bureau, London, and, more recently, a novel method and machine have been designed and operated in Mexico The simple, cheap process devised by the Bureau has proved entirely satisfactory and is now being operated in Central and South America, India, Rhodesia, the Union of South Africa and Yugoslavia. The plant required is inexpensive and the procedures, which can be adapted to meet a variety of conditions, are believed to be eminently suitable for introduction into many endemic goitre areas of the world where large-scale salt-manufacturing facilities do not exist but local sources of crude salts are available.

sizes is withdrawn and placed, while still hot, in wooden moulds where salt in the adherent liquid continues to separate, binding the whole into solid blocks. These can then be thoroughly dried in a hot chamber and subsequently crushed and screened if necessary. This type of salt can also be made free-running by incorporating the requisite amount of magnesium carbonate or other agent which will prevent caking.

The "vacuum" process has advantages over the open-evaporation methods in that it can produce a far greater output of salt at a lower cost and can be operated on a continuous basis, involving the minimum of labour. Even if these advantages did not exist, the fine, uniform grain-size of "vacuum" salt and its free-running property are such considerable marketing assets that they would ensure its successful competition with other grades of salt in communities demanding a high-quality product. In this process, the natural brine is first freed from calcium sulfate and magnesium chloride by treatment with lime and soda ash. It is then run into large, triple-effect evaporators into which live steam is admitted, with the result that the liquid rapidly boils. The steam from the first evaporator is passed into a second and thence into a third evaporator, heating the brine in these also. In the final evaporator, the steam is removed by a pump which reduces the pressure throughout the system in such a way that pressure and temperature are lowest in the third evaporator and highest in the first. The *fine-grained salt which falls to the bottom in all the evaporators is removed* mechanically and conveyed first to hot-air driers and then to screening plant. As an indication of the saving effected, it may be mentioned that whereas one ton of coal is required to produce 2½ tons of open-pan salt, the same weight will produce 5-6 tons of "vacuum" salt, or more if waste steam from another process is available [68] The vacuum process, it should be noted, cannot be used if salt in the form of large crystals is required.

Production of Iodized Salt

In iodizing salt, the object is to add a predetermined, very small proportion of an iodine compound in such a way that it is uniformly and effectively mixed with a very much greater bulk of material so as to produce a homogeneous mixture which is preferably non-caking and, in any case, capable of withstanding any tendency for the constituents to segregate Essentially, there are three methods of achieving this object: spraying, dry-mixing, and the treatment of brine. The processes are inexpensive and comparatively simple, so that effective action by public health authorities, with the support of their governments, can ensure that iodized salt is made available in any part of the world. The method chosen will depend on various factors, such as the quantity and type of salt to be iodized, the customs and preferences of the consuming population, and the economic conditions in the country where the process is operated. Thus, the fine salt

work. The tank is connected to a compressed-air supply to permit the solution to be sprayed at constant pressure and provide accurate control of the process. In the final drier the salt is stirred by paddles attached to a horizontal shaft, and by this operation uniform iodization of the salt is ensured. As the small moisture content resulting from the addition of the spraying solution is completely removed in the drier, the potassium iodide remains in physically intact relation with the salt and is not subject to the segregating effect which may occur in dry-mixed material owing to the difference in the specific gravities of potassium iodide and sodium chloride. The spraying process is decidedly more economic than the dry-mixing process. It also permits easy changes in the level of iodization to accord with the varying requirements of authorities in different parts of the world, as accurate control of the iodine content of the final product may be achieved by adjusting the concentration, volume and pressure of the spraying solution, the diameter of the nozzle orifices, and the speed of the conveyor. Moreover, the product, besides being dry and free-flowing, requires no grinding, sifting, drying, or mixing before being packeted.

In Austria, a portable salt-iodizing machine capable of handling 15 000 kg of salt in 8 hours has been used by the authorities of the Austrian State Salt Works. In this machine, salt is lifted from the stock bunker by means of a bucket elevator on to a conveyor belt which passes under a fine spray of dilute potassium iodide solution. A worm screw then mixes the iodized salt. The potassium iodide solution is delivered drop by drop from a container provided with a narrow-bore outlet pipe and spraying is effected by compressed air. This plant, it seems, was first used in the year 1925.[64]

A larger Austrian plant (Fig. 2), manufactured by Maschinen- und Transportanlagen G m.b H, Stockerau, has an hourly output of 5000 kg The paddle-screw mixer in this plant is about 2 2 m long. The iodizing solution (50 g of potassium iodide in five litres of distilled water) is sprayed on to the salt at a pressure of three atmospheres, and the usual level of iodization is one part of potassium iodide to 200 000 parts of salt.

The iodization process[43] successfully used in the Ural regions of the USSR for fourteen years or more differs in some ways from the British and Austrian methods *In particular, the Russian plant (Fig 3 and 4)* incorporates a crusher into which the potassium iodide solution (25 g of potassium iodide per ton of salt) is sprayed from a curved pipe having eleven nozzles which disperse the solution in the form of a fan-shaped jet. No additional pressure is applied to the tank containing the solution which consequently emerges at a pressure corresponding to the head of liquid. In the crusher, high-speed grinding and mixing proceed simultaneously, while further thorough mixing is effected in the worm-screw conveyor fitted with right- and left-hand paddles into which the salt is discharged. This plant treats 15-20 tons of salt in eight hours. It is simpler and cheaper than

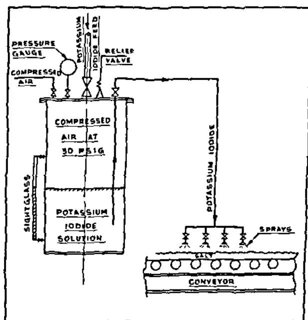
Free-Running Salt

Spraying process

The spraying method, which is continuous, forms part of the routine operation of "vacuum" salt production and is probably the most satisfactory for large-scale practice, although it has been claimed [21] that continuous mixing does not yield so uniform a product as does the batch, dry-mixing method.

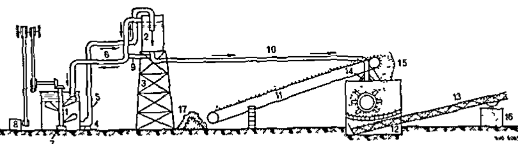
When the salt leaves the vacuum evaporators it is discharged into a rotating filter and then conveyed to a final drier for the complete removal of moisture. Satisfactory and uniform iodization of the salt is achieved by spraying a solution of potassium iodide on to the salt as it passes along a conveyor-belt prior to its entry into the final hot-air drier. The simplicity of the operation is demonstrated in Fig. 1, which shows salt from the vacuum evaporators passing along the conveyor-belt under a series of spray nozzles through which the iodide solution is delivered in the desired proportion.

FIG 1 IODIZATION OF FREE-RUNNING SALT BY SPRAYING WITH POTASSIUM IODIDE SOLUTION



The equipment used in Britain consists merely of a small storage tank for potassium iodide solution, the spray nozzles, and the necessary pipe-

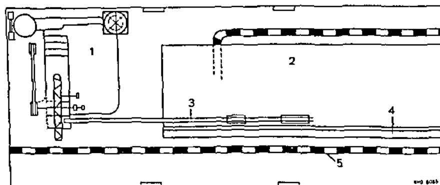
FIG. 3. MANUFACTURE OF IODIZED SALT IN THE URALS



1. *Tank in which potassium iodide is dissolved*
2. *Pressure tank*
3. *Support for pressure tank*
4. *Centrifugal pump*
5. *Delivery pipe*
6. *Overflow pipe*
7. *Washing pipe*
8. *Electric motor for stirrer of iodide tank*
9. *Emergency pipe*
10. *Pressure pipe for potassium iodide solution*
11. *Conveyor belt*
12. *Hammer crusher*
13. *Worm-screw conveyor*
14. *Potassium iodide sprayer*
15. *Hopper for feeding crusher*
16. *Working table*
17. *Stock of dry salt*

Reproduced from Mitjašin[49]

FIG 4 PLAN SHOWING THE ARRANGEMENT OF THE EQUIPMENT FOR THE IODIZATION OF DOMESTIC SALT AT THE MOLOTOV REGIONAL ANTI-GOITRE STATION

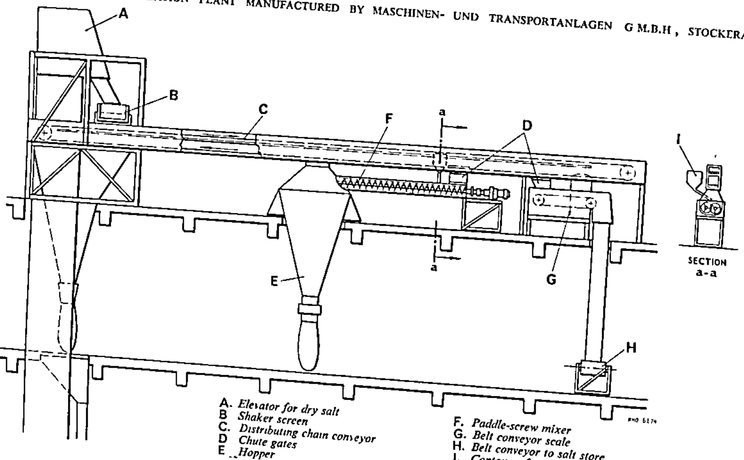


1. *Mixing plant*
2. *Drying chamber for salt*
3. *Conveyor belt*
4. *Rack*
5. *Narrow-guage road*

Reproduced from Mitjašin[49]

the machine installed at Leningrad If the salt produced is properly packed in strong paper bags (usually containing 1 kg) or boxes and kept in dry rooms, the iodide content does not fall below the standard value during six months, but this storage period should not be exceeded

FIG. 2. AUSTRIAN IODIZATION PLANT MANUFACTURED BY MASCHINEN- UND TRANSPORTANLAGEN G.M.B.H., STOCKERAU



Reproduced by courtesy of Maschinen- und Transportanlagen G m b H, Stockerau, Austria

are placed in the mixer and slowly mixed for three minutes. Brine (150 ml) having a specific gravity of 1.110 and containing 1.25 g of potassium iodide is then sprayed on to the salt by means of compressed air at a pressure of two atmospheres, this process occupying two minutes. Mixing is continued for a further five minutes, after which another 200 kg of salt are added and the mixer again set in motion for ten minutes more. It is claimed that salt so treated remains unchanged for months but, apparently, only if very dry salt (moisture content 0.2%-0.3%) is used

Stabilized iodized salt has been prepared by spraying methods In one process, a mixture of potassium iodide, hydrated sodium thiosulfate, and—if the mixture is not sufficiently alkaline—caustic soda is the spraying medium [53] The mixture is maintained at a temperature exceeding 48° C to liberate the water of crystallization of the sodium thiosulfate. This water is sufficient in quantity to dissolve all the constituents and thus provide a liquid medium which is sprayed on the salt as it passes to the final drier. In another process, a portion of the salt to be iodized is sprayed with a solution containing potassium iodide, sodium bicarbonate, and magnesium carbonate.[4] The treated salt is then dry-mixed with the remaining portion of the salt to provide a final product which is claimed to possess the maximum desirable characteristics in regard to stability and uniformity of iodization

Plant for the spraying process is offered for sale at prices ranging from £2500-£3000 (7000-8400 US dollars). One of the manufacturers (in Switzerland) supplies machinery capable of iodizing as much as 4000 kg per hour In this plant, the conveyor band moves at about 1.2 m per second The electric driving motors used are totally enclosed so as to protect them from salt dust, and all the equipment, which is constructed of suitable material, has a thick coating of special varnish to prevent or diminish possible attack by the salt.

Dry-mixing process

The iodization of salt by the direct addition of finely powdered potassium iodide in association with stabilizing and drying agents is a widely adopted procedure and is especially satisfactory for the preparation of relatively small stocks

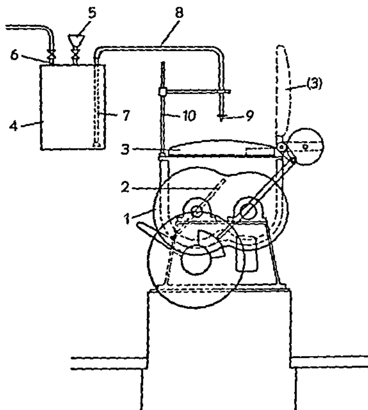
The general method, which is essentially the same as that described first by Hirschfelder [31] and then by Geagley,[21] is to prepare a stock mixture of ground potassium iodide, a stabilizer, and a drying agent such as is usually included in free-running salts. The required quantities of this mixture are then added to batches of salt. Since the amount of drying agent used is considerably greater than the quantity of iodide, this procedure results in a very satisfactory uniformly iodized product.

The quantity of iodide added to the salt will, of course, vary from country to country according to the recommendations of the medical

In another Russian method,[43] based on investigations at the Soviet Central Scientific Salt Research Laboratories, iodization is effected in centrifuges by means of a solution of potassium iodide (concentration, 0.24-0.26 g per litre) but this process appears not to involve spraying The salt used in the investigation contained 4 0%-4.5% of moisture. It was first washed with purified brine in order to prevent accumulation of sodium sulfate. The level of iodization was 1 : 100 000. Spent iodizing solution was re-used several times, best results being obtained with five-fold re-use

Still another spraying process (non-continuous), in which a mixer is used instead of a conveyor, is described in German Patent Specification No. 627,061 of 1936 [58] (Preussische Bergwerks- und Hutten-A.G., Berlin) which also includes a diagram of the machine used (Fig. 5). 200 kg of salt

FIG. 5. MACHINE FOR THE IODIZATION OF SALT USING A MIXER IN PLACE OF A CONVEYOR



1. *Mixer*
2. *Paddles for stirring*
3. *Lid*
4. *Glass container*
5. *Funnel for introducing iodized brine*
6. *Compressed air pipe*
7. and 8. *Delivery tube*
9. *Nozzle*
10. *Movable support around which delivery tube can be rotated*

are placed in the mixer and slowly mixed for three minutes. Brine (150 ml) having a specific gravity of 1.110 and containing 1 25 g of potassium iodide is then sprayed on to the salt by means of compressed air at a pressure of two atmospheres, this process occupying two minutes. Mixing is continued for a further five minutes, after which another 200 kg of salt are added and the mixer again set in motion for ten minutes more. It is claimed that salt so treated remains unchanged for months but, apparently, only if very dry salt (moisture content 0.2%-0.3%) is used.

Stabilized iodized salt has been prepared by spraying methods. In one process, a mixture of potassium iodide, hydrated sodium thiosulfate, and—if the mixture is not sufficiently alkaline—caustic soda is the spraying medium [33] The mixture is maintained at a temperature exceeding 48° C to liberate the water of crystallization of the sodium thiosulfate This water is sufficient in quantity to dissolve all the constituents and thus provide a liquid medium which is sprayed on the salt as it passes to the final drier In another process, a portion of the salt to be iodized is sprayed with a solution containing potassium iodide, sodium bicarbonate, and magnesium carbonate [6] The treated salt is then dry-mixed with the remaining portion of the salt to provide a final product which is claimed to possess the maximum desirable characteristics in regard to stability and uniformity of iodization.

Plant for the spraying process is offered for sale at prices ranging from £2500-£3000 (7000-8400 US dollars) One of the manufacturers (in Switzerland) supplies machinery capable of iodizing as much as 4000 kg per hour. In this plant, the conveyor band moves at about 1 2 m per second. The electric driving motors used are totally enclosed so as to protect them from salt dust, and all the equipment, which is constructed of suitable material, has a thick coating of special varnish to prevent or diminish possible attack by the salt

Dry-mixing process

The iodization of salt by the direct addition of finely powdered potassium iodide in association with stabilizing and drying agents is a widely adopted procedure and is especially satisfactory for the preparation of relatively small stocks

The general method, which is essentially the same as that described first by Hirschfelder [31] and then by Geagley,[24] is to prepare a stock mixture of ground potassium iodide, a stabilizer, and a drying agent such as is usually included in free-running salts The required quantities of this mixture are then added to batches of salt. Since the amount of drying agent used is considerably greater than the quantity of iodide, this procedure results in a very satisfactory uniformly iodized product

The quantity of iodide added to the salt will, of course, vary from country to country according to the recommendations of the medical

authorities, but the following outline, based on a recognized method of manufacture, will serve to indicate the necessary process operations:

97.75 pounds (44.3 kg) of calcium phosphate and 2.2 pounds (1.0 kg) of potassium iodide are mixed together and ground to pass a 100-mesh sieve. One pound (0.45 kg) of this mixture is added to 199 pounds (90.2 kg) of dried salt, which is then mixed for sufficient time to give a uniform product *as determined by analysis. As an added assurance of obtaining a uniform final product, some manufacturers prefer to incorporate the iodide-phos*phate mixture in two stages, first thoroughly mixing it with about 25% of the salt and then adding the remainder of the salt.

Accurate control is essential at each stage of the above process. It is important that the master-batch be carefully analysed for uniformity of iodine content, a number of samples of the finished product should be tested from each batch.

Commercial phosphate mixes better with salt than do most drying agents and it also has some value as a mineral dietary adjunct. A special grade of basic tricalcium phosphate, with a composition approaching $Ca_3(PO_4)_2$ $Ca(OH)_2$, is manufactured *for use in the preparation of iodized salt.*[1] *This* substance is more alkaline than ordinary commercial calcium phosphate and its use is claimed to confer enhanced stability and improved free-running qualities. However, a wide variety of other materials can be used as iodized-salt conditioners. They include magnesium carbonate, sodium bicarbonate, sodium carbonate, calcium carbonate, activated carbon,[20] and, for iodized cattle licks, even viscous sugar syrup.[66] One satisfactory process utilizes a mixture of 90% by weight of potassium iodide, 8% of calcium carbonate, and 2% of calcium oxide.[69]

Excellent stabilization can be achieved also by the University of Wisconsin process,[29] which consists in the addition of small quantities of sodium carbonate, starch and sodium thiosulfate. Another widely adopted method of ensuring the stabilization of iodized free-running salt produced by the dry-mixing process for livestock is to mill calcium stearate with the potassium iodide whereby the water-insoluble stearate surrounds each particle of the powdered iodide and protects it from moisture.[34] Although calcium stearate is non-toxic and may be ingested in reasonable amounts with complete safety, it could be used for human consumption only if permitted by health authorities.

In the USSR[84] *tests with apparatus for dry-mixing* led to the conclusion that centrifugal and cascade mixers were more economical than barrel mixers and also that the best method of preparing the stock mixture was to add a small amount of potassium iodide solution to dry salt.

The difficulties involved *in dry-mixing very unequal quantities* of two solids have been discussed by Bloom & Livesay[8] who have also provided a mathematical model for calculating the particle size necessary to ensure even distribution at various levels. In this connection, it is worthy of note

that both potassium iodide (specific gravity 3.13) and potassium iodate (specific gravity 3.89), the compounds most commonly used for iodization are appreciably heavier than sodium chloride (specific gravity 2.16). (In *France, salt may be iodized with sodium iodide which has a specific gravity* of 3.7)

Treatment of Brine

A third, though less important, method of iodizing salt is to add potassium iodide solution to the brine during production of open-pan salt in such a way that a predetermined concentration of the iodide is maintained in the mother-liquor throughout the evaporation process. To achieve satisfactory results it is necessary to maintain accurate analytical control, and the method is suitable only when skilled labour and adequate laboratory facilities are available

In the continuous open-pan evaporation of brine the salt crystals forming at the bottom of the pan are removed at frequent intervals by means of perforated shovels and allowed to drain on the floor or on racks placed beside the pans A certain proportion of mother-liquor remains adherent to the salt crystals, and, taking advantage of this fact, the process provides for the iodization of salt by the addition of potassium iodide to the original brine in such a proportion that the final volume of mother-liquor adherent to the salt contains sufficient iodide to give the desired level of iodization.[51] The proportion of adherent brine will depend on the precise conditions adopted for salt production When this figure has been ascertained by routine tests, it requires only a straightforward calculation to determine the potassium iodide content that must be maintained in the mother-liquor. It is preferable to pump the potassium iodide solution into the brine supply before delivery into the evaporating-pan If the feed and evaporation rates are carefully controlled, very uniform iodization of the salt can be achieved.

By a similar technique it is also possible to iodize salt produced by batch open-pan evaporation of brine, and this method has been adopted in Colombia [25] To each batch of brine, dilute potassium iodide solution is added in such quantity that the small volume of mother-liquor remaining adherent to the final salt product removed from the pan contains the necessary concentration of iodide to provide the desired level of iodization in the salt. The residual mother-liquor in the pans is re-used with further stocks of fresh brine and thus no loss of iodide is incurred

The need for skilled supervision renders the above type of iodization process more expensive than dry-mixing and it cannot be regarded as suitable for general adoption

If it were possible to discover a cheap, harmless iodine compound which would crystallize from brine together with salt and in the required very low proportions, iodized salt could be produced directly from the brine, and dry-mixing, spraying and the form of brine treatment just described

would be unnecessary. Inorganic iodine compounds, however, have inappropriate solubilities, are poisonous, are too expensive, or are otherwise unsuitable; and it seems probable that organic compounds would suffer from similar disadvantages

Crystalline Salt

Dry-mixing process

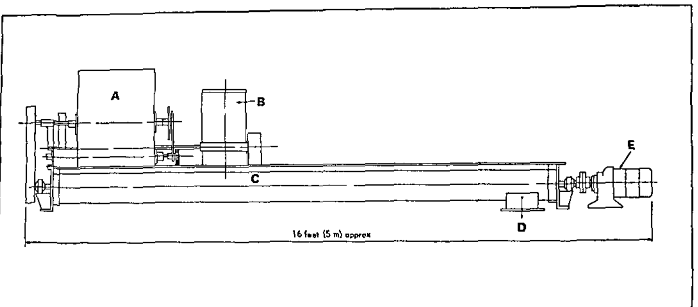
Most of the salt consumed throughout the world is crystalline salt obtained by heated open-pan or solar evaporation of brines. Indeed, the *fine free-running salt regarded* as a domestic necessity in countries with high living standards is quite unfamiliar to most of the inhabitants of the world It would be too expensive for their use even if it could be made available and, in some cases at least, the salt producers and sellers as well as the population would regard it with misgiving or might even resist using it.

The iodization process devised by the Chilean Iodine Educational Bureau, London, and the Mexican process, both of which take account of these points, have already been mentioned. These processes, and the machines used, will now be described

The flow-sheet in Fig 6 illustrates the straightforward layout and method of operating a plant designed by W. Gardner & Sons Limited, Gloucester, England, to produce about 10 tons (10 000 kg) of iodized salt in a working day. The present cost of the complete plant is about £420 (1175 US dollars) Where greater outputs are required, plants of similar design but capable of producing up to 25 tons (25 000 kg) per day can be supplied at a slightly higher price.

Coarse crystalline salt is fed into the hopper of the bulk feeder at the rate of approximately 1 ton (1000 kg) per hour and passes into the enclosed worm-screw mixing-conveyor. At a point near the base of the bulk feeder, a mixture of one part of powdered potassium iodide or potassium iodate and ten parts of calcium carbonate, or any available inert free-flowing powder, is introduced into the worm-screw mixing-conveyor through a precision feeder at the necessary rate to provide a final product containing the desired proportion of iodine. The calcium carbonate or other inert powder is added to the iodide or iodate to provide a greater bulk of material for passage through the precision feeder and thus to facilitate control of the degree of admixture of the iodizing agent with the salt. At a level of approximately 20 ounces (570 g) of potassium iodide mixture per hour, the final product would contain about 1 part by weight of potassium iodide per 20 000 parts by weight of salt. If potassium iodate mixture is employed, approximately 26 ounces (740 g) per hour are required to provide the same level of iodization. For reasons which will be given later, it is recommended that potassium iodate should be used in circumstances where the iodized salt is likely to be stored under humid or other adverse climatic conditions.

FIG. 6. OPERATION FLOW-SHEET FOR IODIZATION OF COARSE SALT



A. *Bulk feeder for salt*
B. *Precision feeder for iodine compound*
C. *Mixing conveyor*
D. *Iodized salt*
E. *Driving motor*

Reproduced by courtesy of W Gardner & Sons Limited, Gloucester, England

The salt and the iodide or iodate mixture are intimately combined during their passage along the remaining length of the worm-screw mixing-conveyor, which is fitted with right- and left-hand paddles to give an efficient mixing action to the product passing along the worm. The iodized salt is collected directly in bags or other containers at the end of the conveyor and the whole operation of the plant requires the minimum of skilled labour.

The worm-screw of the conveyor and the agitator of the bulk feeder are driven by single belts from a shaft attached to a small electric motor (1.5-HP) or an internal combustion engine, and the rate of throughput of salt can be adjusted in a few minutes by manipulating a ratchet mechanism on the end of the bulk feeder. This mechanism controls the speed of the worm conveyor.

The simplest means of operating the precision feeder used to add iodide or iodate mixture to the salt is a pulley-drive from the main shaft. The use of multiple pulleys permits the adjustment of the precision feeder to six different speeds to accord with varying throughputs of salt.

If desired, the precision feeder can be operated independently by gearing to a 0.25-HP electric motor, as shown in Fig. 7 and 8 of the plant supplied by Novadel Limited, London, England, for the production of iodized salt in Guatemala. In this case the feeder can be set at any desired rate by varying the gear wheels, and five sets of wheels are supplied with the feeder for this purpose. (Novadel's plant has recently been improved and the cost has been reduced by about 10%).

A second type of plant, which operates on the same principles but differs in layout, has been constructed by Arenco-Alite Limited, Letchworth, Herts., England, for use in the Union of South Africa. At the request of the authorities, this has been assembled on a light metal frame in order that it can be lifted by porters and also carried on a lorry without being dismantled. A view of this plant is provided in Fig. 9.

Fig. 10 shows a general view of a plant for iodizing coarse salt that has recently been installed by the Government of India at Sambhar. This plant is of particular interest because, like the Soviet plant, it combines a unit for crushing the salt with the usual iodization unit.

Spraying process

A continuous spraying process which can be used with crude salt, such as that produced by solar evaporation, as well as with refined salt has been described recently by Dr Herbert Stacpoole,[71] chief of the Mexican Anti-Goitre Campaign, who has also designed a simple, cheap, portable machine for the purpose. This machine is illustrated in the accompanying figures (11 and 12).

Stacpoole regards dry-mixing as too expensive because of the long period of agitation required to ensure uniform distribution of the iodizing

FIG 7. GENERAL VIEW OF PLANT FOR IODIZING SOLAR-EVAPORATED SALT IN GUATEMALA

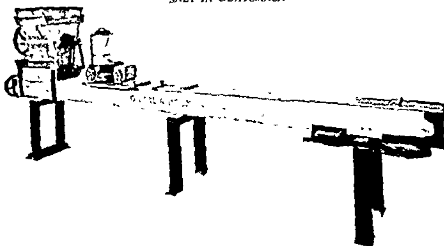
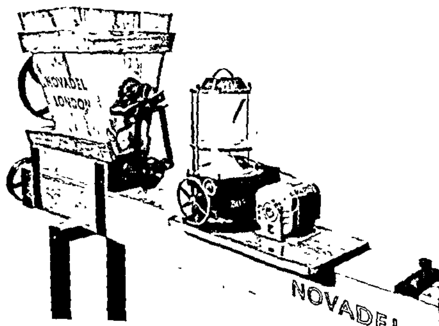


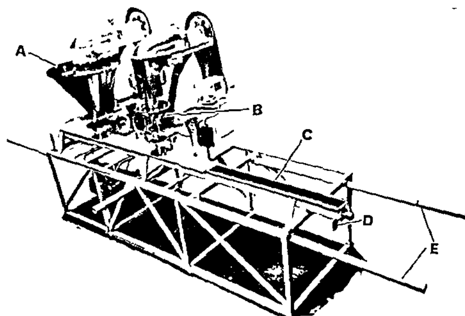
FIG 8 VIEW OF SECTIONS OF IODIZING PLANT IN GUATEMALA



The bulk controller (left) and the precision feeder (centre) control the throughput of salt and the level of iodization, respectively.

Reproduced by courtesy of Novadel Limited, London

FIG. 9. TRANSPORTABLE EQUIPMENT DESIGNED FOR THE TREATMENT OF SALT IN THE UNION OF SOUTH AFRICA



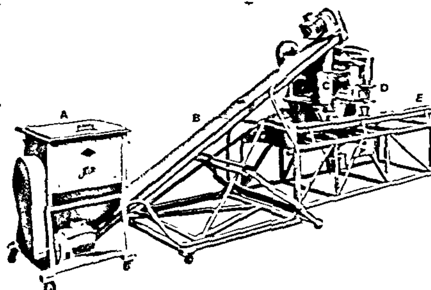
A. *Bulk hopper for salt*
B. *Bulk hopper for iodine compound*
C. *Blending-conveyor trough*
D. *Outlet*
E. *Lifting-handles in extended position*

Reproduced by courtesy of Arenco-Alite Machines Limited, Letchworth, Herts, England

agent and he also believes that the mixture obtained is not homogeneous if a worm-screw, which must be long and must move rapidly, is used for mixing. In addition, he objects to the use of a conveyor-belt, since it permits iodization of the surface of the salt layer only. His plant operates as follows (Fig 12):

The salt to be iodized is deposited in a wooden hopper (1) lined with aluminium sheet. The base of this hopper, which holds about 100 kg, forms a semi-circular trough in which turns a corrosion-resistent (stainless steel) worm-screw (2). This serves to carry the salt into the base of an elevator (3) which consists of a rubber belt (4) carrying aluminium buckets (5). The elevator is driven by an aluminium pulley (6) attached to the shaft of a 2-HP electric (or other) motor. The casing of the elevator is made of wood protected inside and outside with oil paint; the wooden base, which has two doors for inspection and cleaning, is lined with aluminium. The elevator raises the salt about 3 m, discharging it into an aluminium-lined hopper (7) from which it drops through a rotating sluice (8) made of aluminium and stainless steel into the iodizing chamber (10). A link-belt

FIG. 10. COMBINED CRUSHING AND IODIZING PLANT FOR PROCESSING CRUDE SALT AT SAMBHAR, INDIA



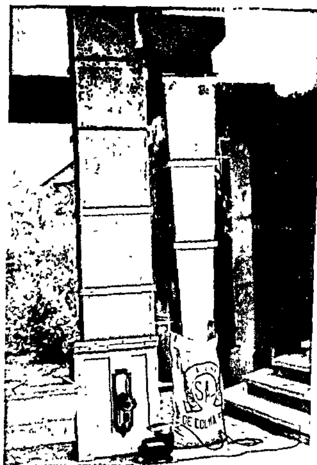
A. *Crushing equipment*
B. *Elevator to iodizing unit*
C. *Hopper for salt*
D. *Hopper for iodizing agent*
E. *Blending-conveyor trough*

Reproduced by courtesy of Arenco-Alite Machines Limited, Letchworth, Herts, England

and cog-wheel connected to the upper pulley of the elevator serve to drive the sluice above which turns a stirrer (9) serving to maintain an uninterrupted flow of salt to the sluice. The rate of flow of salt through the sluice is constant but can be regulated by changing the diameter of the cog-wheel that turns the shaft to which it is attached.

The iodizing chamber, which is constructed of aluminium lined with plastic or of wood lined with aluminium, has the shape of an elongated pyramid about 2.24 m high by 0.5 m at the top and 0.3 m at the lower end. Close to the upper end there is a grill (11) made of aluminium which scatters the salt so that it falls as a continuous shower. In this way, provision is made for ensuring intimate contact of the grains of salt with the droplets of iodate solution which are injected upwards with a spray gun (12) fixed just above the outlet (13) of the chamber. The iodate solution from a tank and compressed air are delivered to the gun through two hoses (14), pressure being provided by a $^1/_3$-HP motor. The gun is set so that the number of millilitres of iodate solution delivered per minute equals the number

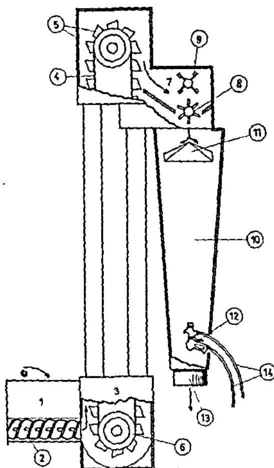
FIG. 11. SALT-IODIZING MACHINE DESIGNED BY DR H. H. STACPOOLE



(usually 85-93) of kilograms of salt which falls in the same time. Experience has shown that 1 ml of spray is enough to iodize uniformly 1 kg of salt whether it be coarse, ground, or free-running. Five metric tons of salt can be iodized per hour.

Stacpoole points out that, where salt is delivered by truck, it may be more convenient and cheaper to eliminate the elevator and to have the trucks drive up a ramp to discharge to an inclined platform adjacent to the hopper at the top of the iodizing machine (Fig. 13). He also insists that iodate should be used as iodizing agent. His machines have now been in successful operation in Mexico for some time, producing iodized salt which is readily accepted by the population although opposition to iodization by producers and sellers had previously been encountered

FIG. 12. DIAGRAM SHOWING THE OPERATION OF THE SALT-IODIZING MACHINE DESIGNED BY DR H. H. STACPOOLE

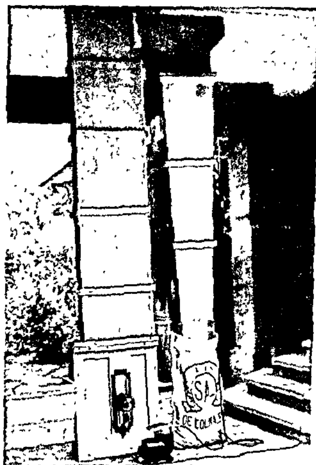


For key to the numbers see text (page 428)

Stability of Iodized Salts

Reference has been made above to the addition of stabilizers and drying agents to iodized salt to prevent or restrict the losses of iodine which may otherwise occur For two reasons, it is important that iodized salt should remain stable during storage. First, it is necessary that iodized salt should contain the actual proportion of iodine stipulated by the medical authorities. Secondly, manufacturers must be able to feel assured that their products will fulfil government regulations controlling the level of iodization. A very comprehensive survey was made by Kelly [35] in 1953 of factors affecting the

FIG. 11. SALT-IODIZING MACHINE DESIGNED BY DR H. H. STACPOOLE



(usually 85-93) of kilograms of salt which falls in the same time. Experience has shown that 1 ml of spray is enough to iodize uniformly 1 kg of salt whether it be coarse, ground, or free-running Five metric tons of salt can be iodized per hour.

Stacpoole points out that, where salt is delivered by truck, it may be more convenient and cheaper to eliminate the elevator and to have the trucks drive up a ramp to discharge to an inclined platform adjacent to the hopper at the top of the iodizing machine (Fig. 13). He also insists that iodate should be used as iodizing agent His machines have now been in successful operation in Mexico for some time, producing iodized salt which is readily accepted by the population although opposition to iodization by producers and sellers had previously been encountered

(*e*) has an acid reaction;

(*f*) contains impurities derived from the mother-liquor.

The Czechoslovak workers found that loss of iodine was greater when the level of iodization was 25 mg of potassium iodide per kg of salt than when it was 12 mg

Very recently, a thorough study of factors affecting the stability of iodized salts was made by Plíška [56] in the faculty of food technology of the Chemical-Technical College of Prague. He maintains that the role of moisture has been, to some extent, misunderstood, since, according to Zinovjev,[83] the surface layer of common salt may bind as much as 12% of moisture. Tests were conducted on salt to which small proportions (0.1%, 0.2%, 0.5%, 1.0%, 2.0% and 4.0%) of one of five inorganic compounds (aluminium sulfate, calcium chloride, magnesium chloride, potassium chloride, sodium sulfate) had been added and which had been iodized either with potassium iodide or with potassium iodate and stored for periods of up to one year at 17.5°-21.0° C in atmospheres having various relative humidities The effects of the five compounds on aqueous solutions of the iodide and iodate were also examined On the basis of the findings, Plíška reached the following conclusions.

(1) some cations (Al, Mg, Ca) have a powerful moistening effect because their salts undergo slight hydrolysis with production of hydrogen ions (acidity) and consequent oxidation (of iodide) by atmospheric oxygen,

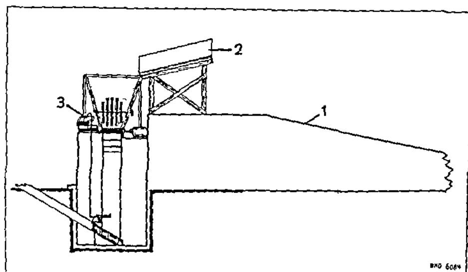
(2) traces of ions of ferric iron, iodate, and nitrite have a direct, very destructive effect on iodide and the ferric and nitrite ions also have a catalytic action,

(3) potassium ions and sulfate ions have a stabilizing effect (very probably because they inhibit moistening),

(4) iodate is more stable in common salt than is iodide but should be used only when the iodide which it would replace would be liable to suffer large losses.

From consideration of these points it is apparent that the stable iodization of fine grades of pure salt produced by vacuum evaporation can be accomplished without difficulty Such salts are completely dried during manufacture, are packed in special containers and are effectively stabilized by the presence of the alkaline non-caking agents which are added to preserve their free-running properties. If they are stored satisfactorily under reasonable conditions of temperature and humidity they remain stable for considerable periods The table on page 434 shows the results of determinations of iodine contents of some samples during a trial extending over nearly two years No reduction in the iodine content of the salt occurred during this period

FIG. 13. A MODIFICATION OF DR H. H. STACPOOLE'S SALT-IODIZING MACHINE WITH RAMP INSTEAD OF ELEVATOR



1. *Ramp for trucks*
2. *Platform for unloading salt*
3. *Compressor*

stability of salt iodized with potassium iodide, potassium iodate, dithymol di-iodide, or an organic iodide complex, and investigations on this problem have since been carried out in Bali,[79] Czechoslovakia,[59] French West Africa,[75] Romania,[72] the USSR,[28, 55, 67], and Venezuela.[15] The results show that losses of iodine do not occur in salt iodized with potassium iodide if the salt:

(*a*) is reasonably dry and free-running;

(*b*) is packed in containers with impervious linings;

(*c*) is stored in the dark;

(*d*) is kept cool;

(*e*) contains a stabilizing agent;

(*f*) is free from impurities

Losses are liable to occur if the salt:

(*a*) is not dried during production;

(*b*) is exposed to humid atmospheres or excessive aeration;

(*c*) is exposed to sunlight;

(*d*) is subjected to heat;

affected by oxidizing impurities which may cause decomposition of potassium iodide A further important advantage of potassium iodate is its low *solubility in water* compared with the high solubility of potassium iodide. If packages of salt iodized with potassium iodide become damp, the iodide is attracted to the areas of high moisture content and thus migrates from the body of the salt to the cardboard or fabric of the container. This results in a loss of iodide from the mass of salt with a consequent reduction of its general iodine content Because of its low solubility, potassium iodate migrates much less readily or not at all. It is, in fact, not easily removed from iodized salt even by leaching with water, and for this reason salt containing iodate is satisfactory for the manufacture of salt licks for cattle although these are exposed to all manner of weather conditions.[16] That the stability of iodate in crude table salt is equally satisfactory in the tropics was shown not long ago by Arroyave, Pineda & Scrimshaw [4] who stored a 50-kg sample (added iodine content 1: 10 000) in a hemp fibre sack in an open room for eight months, four of which were dry and four rainy; they found that the loss of iodate in that period was only 3 5% although the average humidity had ranged from 70% to 84% Moreover, no significant redistribution of the iodate took place Similarly, in Venezuela, Andrade [2] and his co-workers noted that table salt iodized with sodium iodate lost no iodine during one year and crude salt lost only 20%, while in Brazil, Paulini & Pereira [54] found that potassium iodate likewise resisted decomposition in common salt for a year at least, although they found that it migrated to some extent if the humidity were high

The effects of long-term ingestion of potassium iodate have not yet been fully revealed, but it is known that large single doses can be tolerated [13] and that the compound is rapidly broken down in the body, providing a source of iodine available to the thyroid gland for hormone formation both in man [50] and in animals [82] It is quite reasonable to assume, therefore, that iodate can safely be used in the minute proportions required for the iodization of salt and, in fact, experience in Mexico,[70] where iodated salt was introduced in 1952, as well as in El Salvador, Guatemala [65] and India [74] has shown, not only that no ill effects have resulted from the large-scale administration of the salt (or of tablets containing the compound) but that the effects have been beneficial. Accordingly, it is recommended that iodate should be used in all circumstances where the type of salt available or the environmental conditions could cause loss of iodine from salt iodized with potassium iodide

It may be added that, for human consumption at least, dithymol diiodide cannot seriously be considered as an iodizing agent for large-scale use, and presumably this applies to organic iodide complex also. It is possible, however, that cuprous iodide,[49] which forms a constituent of some mineral supplements for animals, might be employed if it were found to be acceptable. It has the advantage of being only very slightly soluble in water.

STORAGE TESTS ON IODIZED SALT *

		Iodine content		
		µg per ounce **	% by weight	proportion I NaCl
Specification		425-652	0 0015-0 0023	1·66 600—1, 43 500
Mean		538	0 0019	1 52 600
Analysis by maker on issue (28 3 51)		538	0 0019	1·52 600
A(1) Stored on open shelf above sink until 5 7 51				
After 3 months (5 7 51)	Top	567	0 0020	1 50 000
	Middle	567	0 0020	1, 50 000
A(2) Remaining contents of packet A(1) opened on 5 7 51 were re-mixed and replaced on shelf with top of packet *fully* open until 19 2 52 Some caking at top of sample in February 1952				
After 10 months (19 2 52)	Top	567	0 0020	1:50 000
	Middle	538	0 0019	1, 52 600
B Stored in dry cupboard until 19 2 52 No caking				
After 10 months (19 2 52)	Top	567	0 0020	1·50 000
	Middle	567	0 0020	1·50 000
	Bottom	510	0 0018	1 55 500
C Stored on open shelf above sink until 19 2 52 No caking				
After 10 months (19 2 52)	Top	538	0 0019	1, 52 600
	Middle	538	0 0019	1 52 600
	Bottom	538	0 0019	1 52 600
D Stored in dry cupboard until 3 1 53 No caking				
After 21 months (3 1 53)		525	0 00185	1, 54 000

* Delivered for independent analysis [illegible]

On the other hand, the stabilization of salts produced by open-pan and solar evaporation presents some problems as these salts may contain both moisture and impurities. Furthermore, they are frequently stored in bulk or packed in ordinary hessian bags. They may also be exposed to adverse climatic conditions. It is recommended, therefore, that open-pan and solar salts should be iodized by the addition of potassium iodate, which can effectively replace potassium iodide for the biochemical synthesis of thyroxine Potassium iodate is an extremely stable compound and not liable to be

affected by oxidizing impurities which may cause decomposition of potassium iodide. A further important advantage of potassium iodate is its low solubility in water compared with the high solubility of potassium iodide If packages of salt iodized with potassium iodide become damp, the iodide is attracted to the areas of high moisture content and thus migrates from the body of the salt to the cardboard or fabric of the container. This results in a loss of iodide from the mass of salt with a consequent reduction of its general iodine content. Because of its low solubility, potassium iodate migrates much less readily or not at all. It is, in fact, not easily removed from iodized salt even by leaching with water, and for this reason salt containing iodate is satisfactory for the manufacture of salt licks for cattle although these are exposed to all manner of weather conditions.[16] That the stability of iodate in crude table salt is equally satisfactory in the tropics was shown not long ago by Arroyave, Pineda & Scrimshaw [4] who stored a 50-kg sample (added iodine content 1 . 10 000) in a hemp fibre sack in an open room for eight months, four of which were dry and four rainy, they found that the loss of iodate in that period was only 3 5% although the average humidity had ranged from 70% to 84% Moreover, no significant redistribution of the iodate took place. Similarly, in Venezuela, Andrade [2] and his co-workers noted that table salt iodized with sodium iodate lost no iodine during one year and crude salt lost only 20%, while in Brazil, Paulini & Pereira [54] found that potassium iodate likewise resisted decomposition in common salt for a year at least, although they found that it migrated to some extent if the humidity were high

The effects of long-term ingestion of potassium iodate have not yet been fully revealed, but it is known that large single doses can be tolerated [13] and that the compound is rapidly broken down in the body, providing a source of iodine available to the thyroid gland for hormone formation both in man [50] and in animals [82] It is quite reasonable to assume, therefore, that iodate can safely be used in the minute proportions required for the iodization of salt and, in fact, experience in Mexico,[70] where iodated salt was introduced in 1952, as well as in El Salvador, Guatemala [65] and India [71] has shown, not only that no ill effects have resulted from the large-scale administration of the salt (or of tablets containing the compound) but that the effects have been beneficial Accordingly, it is recommended that iodate should be used in all circumstances where the type of salt available or the environmental conditions could cause loss of iodine from salt iodized with potassium iodide

It may be added that, for human consumption at least, dithymol diiodide cannot seriously be considered as an iodizing agent for large-scale use, and presumably this applies to organic iodide complex also It is possible, however, that cuprous iodide,[49] which forms a constituent of some mineral supplements for animals, might be employed if it were found to be acceptable It has the advantage of being only very slightly soluble in water

STORAGE TESTS ON IODIZED SALT *

		Iodine content		
		µg per ounce **	% by weight	proportion I: NaCl
Specification		425-652	0.0015-0.0023	1: 66 600—1: 43 500
Mean		538	0.0019	1: 52 600
Analysis by maker on issue (28.3.51)		538	0.0019	1: 52 600
A(1) Stored on open shelf above sink until 5.7.51				
After 3 months (5.7.51)	Top	567	0.0020	1: 50 000
	Middle	567	0.0020	1: 50 000
A(2) Remaining contents of packet A(1) opened on 5.7.51 were re-mixed and replaced on shelf with top of packet *fully open* until 19.2.52 Some caking at top of sample in February 1952				
After 10 months (19.2.52)	Top	567	0.0020	1: 50 000
	Middle	538	0.0019	1: 52 600
B Stored in dry cupboard until 19.2.52 No caking				
After 10 months (19.2.52)	Top	567	0.0020	1: 50 000
	Middle	567	0.0020	1: 50 000
	Bottom	510	0.0018	1: 55 500
C Stored on open shelf above sink until 19.2.52 No caking				
After 10 months (19.2.52)	Top	538	0.0019	1: 52 600
	Middle	538	0.0019	1: 52 600
	Bottom	538	0.0019	1: 52 600
D Stored in dry cupboard until 3.1.53 No caking				
After 21 months (3.1.53)		525	0.00185	1: 54 000

* Delivered for independent analysis in 7-lb. (3.2-kg) lots in cotton bags Repacked on 3.4.51 by analyst into 1-lb (0.45-kg) cardboard unlined packets supplied by makers The packets were sealed in the usual manner and were stored as shown above 25-g portions were subsequently taken from top, middle, and bottom sections of the packets for analysis.

** 1 ounce = 28.35 g

On the other hand, the stabilization of salts produced by open-pan and solar evaporation presents some problems as these salts may contain both moisture and impurities. Furthermore, they are frequently stored in bulk or packed in ordinary hessian bags. They may also be exposed to adverse climatic conditions. It is recommended, therefore, that open-pan and solar salts should be iodized by the addition of potassium iodate, which can effectively replace potassium iodide for the biochemical synthesis of thyroxine. Potassium iodate is an extremely stable compound and not liable to be

in different regions, and the results obtained in America by the use of salt iodized to this level

It is obviously impossible to fix a standard level of iodization for adoption by all countries. In selecting a local or national level, public health authorities must study the average *per caput* salt consumption, the prevailing dietary standards, the possible existence of goitrogenic factors and the experience of similar areas Their recommendations should ensure that, taking full account of these factors, a *minimum* amount of 150 μg of iodine is available in the quantity of salt utilized in the individual daily diet It must be stressed that in adverse circumstances this quantity may be insufficient and it is desirable that in areas of low dietary standards 300-400 μg of iodine should be available in the estimated daily individual intake of iodized salt

Determination of Iodine in Iodized Salt

Reliable and accurate methods for determining the iodine content of iodized salt are essential both to the manufacturer and to the distributor. The manufacturer must be able to feel confident that the product leaving his factory conforms to the requirements of the authorities, and the distributor must feel assured that the quality of the product standing in his warehouse or shop can be checked rapidly and efficiently at any time

Studies of techniques for the accurate determination of iodine in iodized salt have accordingly been made by workers in countries where iodized salt has been introduced as an agent for the prevention of goitre The method devised by von Fellenberg [22] has been gradually modified and improved by Werner,[80] Andrew & Mandeno,[3] Reith [61] and other subsequent investigators [53] to result in the two official methods [76] at present accepted by the Association of Official Agricultural Chemists in the USA. Before these methods were accepted, the reproducibility of their results had been submitted to very rigorous checking [32] and since other micro-methods, such as the neutron-activation procedure, do not appear to show any advantages [a] it is recommended that they should be used in all countries to facilitate direct comparisons of the iodine contents of local iodized salts Details of the methods are as follows

Method A Dissolve 50 g of iodized salt in distilled water and make up to 250 ml in a volumetric flask. Pipette 25 ml into a 600-ml beaker and dilute to about 300 ml Neutralize to methyl orange with phosphoric acid and then add 1 ml in excess

Add an excess of bromine water, boil gently until colourless and then for five minutes longer Add a few crystals of salicylic acid and cool the solution to about 20°C Add 1 ml of 85% phosphoric acid and about 0 5 g of

[a] The polarographic method of Pliška & Rykl [47] shows promise, however, and may prove to be the best of the micro-methods

Level of Iodization

The proper proportion of iodine required to be present in iodized salt is determined by two fundamental quantitative factors:

1. The average daily dose of iodine per head necessary to prevent goitre in a community (This proportion is then added to the average quantity of salt consumed) It is not possible to state the exact iodine requirement of the human body, but the available evidence suggests that in endemic goitre areas each person should receive a daily dietary supplement of about 150 μg of iodine. Where goitrogenic factors occur, it may be necessary to increase the supplement to 300-400 μg

2. The average amount of food salt consumed per head per day by the community to be treated. This depends on

(a) racial, climatic and other similar considerations. For example, the *per caput* consumption of salt is greater in tropical than in temperate climates;

(b) whether *all* food salt is to be iodized (i e., cooking salt, table salt, and salt used by food industries for making bread, cheese and other processed food) or whether only table salt is to be treated

There is accordingly a wide variation in the levels of iodization which have been officially recommended and adopted in various countries. They range from 1 part of iodide in 10 000 parts of salt to 1 part of iodide in 200 000 parts of salt [11]

The 1 : 10 000 level used in the USA, Canada and most countries in Latin America is the outcome of a long practical clinical experience with a dose of 500 μg of iodine (equivalent to 650 μg of potassium iodide) per head per day, and an estimated average *daily individual consumption of 6 5 g of table* salt.[7] The levels in European countries, on the other hand, are based on estimates of 100-150 μg of iodine as the body's actual physiological requirement, and for this reason are lower than the American level.

In Switzerland, the level is 1 part of potassium iodide in 100 000 parts of salt, based on the iodization of *all* food salt and its consumption at the rate of 10 g per head per day In the United Kingdom, where only table salt is iodized, the recommended level is 1 part of potassium iodide in 40 000 parts of salt In other countries, notably New Zealand, where the goitre problem has been tackled most energetically, the standard level is 1 part of potassium iodide in 20 000 parts of table salt. Allowing for inevitable wastage this is probably the most satisfactory general level of iodization for salt in countries with moderate goitre incidence. In areas of high incidence, the level of 1: 10 000 is preferable, taking into consideration the possible prevalence of goitrogenic factors in some localities, variations in the consumption of salt

may be present in common unrefined salts For this purpose it is recommended that the method of Rogina & Dubravčić [62] should be adopted. This method is extremely sensitive and permits the determination of iodine in common salt through the range 0 to 500 μg of iodine per kg of salt, with a maximum error of ±10 μg of iodine. It is based on the catalytic effect of iodides on the reduction of ceric sulfate with arsenious acid in sulfuric acid solution. The rate of reduction is determined by stopping the reaction at a standard time by the addition of ferrous and thiocyanate solutions and then measuring the resulting red colour of ferric thiocyanate by means of a photometer The method thus differs from the well-known Chaney procedure for the determination of iodine in body fluids in which the rate of reduction is measured while the reaction is in progress. The original report [19] giving full details of the method indicates also corrections to be made when certain impurities, such as ferric salts or bromides, are present in the salt. The method is suitable for the determination of iodine in saline deposits and in sea-water

REFERENCES

1. Adler, H (1947) *Stable iodized calcium phosphate*, US Pat No. 2,417,804
2. Andrade, J L, Feo de Berti, L. A, Brunetti, G, & Antuñez, M (1955) *Memorias del IV Congreso Venezolano de Ciencias Médicas*, 7, 398
3. Andrew, R L, & Mandeno, J L (1935) *Analyst*, 60, 801
4. Arroyave, G, Pineda, O. & Scrimshaw, N S (1956) *Bull. Wld Hlth Org*, 14, 183
5. Badger, W L. & Baker, E M (1941) *Inorganic chemical technology*, New York
6. Berry, R. E (1940) *Iodised salt*, US Pat No 2,205,872
7. Bing, F C (1942) *Fed Proc*, 1, 336
8. Bloom, C & Livesay, E F (1953) *Manufact. Chem*, 24, 371
9. Boussingault, J B J D (1831) *Ann Chim. Phys*, 48, 41
10. *Chem Trade J* (1958), 143, 447
11. Chilean Iodine Educational Bureau (1946) *World goitre survey*, London
12. Clements, F W & Hercus, C (1958) Personal communication
13. Comas y Martinez, L. (1933-34) *Tuberculosis (Habana)*, 5, 1
14. Coulaud, E (1925) *Rev Hyg*, 47, 5
15. Daum, M G (1955) *Arch venez. Nutr*, 6, 175
16. Davidson, W M, Finlayson, M M & Watson, C J (1951) *Sci Agric.*, 31, 148
17. De Josselin de Jong, R (1952) *Doc Med geogr Trop. (Amst)*, 4, 370
18. Donath, W F (1929) *Meded Dienst Volksgezondh Ned-Ind*, 18, 402
19. Dubravčic, M (1955) *Analyst*, 80, 146
20. Engels, W H. (1948) *Iodized salt composition*, US Pat No. 2,452,641
21. [illegible]
22. [illegible]
23. [illegible]
24. [illegible]
25. [illegible] *Industr. (Bogotá)*, 1, Nos 3/4, 21
26. Grange, J (1849) *C R Acad Sci. (Paris)*, 29, 695
27. Greenwald, I (1958) *Lancet*, 1, 1071
28. Gurevich, G P, Zhabskaya, A. K, Mezhvinskaya, E. A (1953) *Vop Pitan*, 12, No 1, 84

potassium iodide. Titrate the liberated iodine with 0.005N sodium thiosulfate

Method B. Dissolve 50 g of the salt sample in water and make up to 250 ml in a volumetric flask. Pipette 50 ml of the solution into a 200-ml Erlenmeyer flask, and neutralize to methyl orange with 2N sulfuric acid. Add bromine water dropwise from a burette in a quantity equivalent to 20 mg of bromine After a few minutes, destroy the greater portion of the remaining free bromine by adding 1% sodium sulfite solution dropwise while mixing Wash down the neck and sides of the flask with water and complete the removal of the free bromine by addition of 1 or 2 drops of 5% phenol solution.

Add 1 ml of 2N sulfuric acid and 5 ml of 10% potassium iodide solution. Titrate the liberated iodine with 0 005N sodium thiosulfate solution adding 1 ml of starch indicator near the end of the titration (1 ml of 0 005N sodium thiosulfate ≅ 0 1058 mg of iodine ≅ 0 1388 mg of potassium iodide)

The determination should be corrected by a blank test of the reagents One or more control determinations should be made for comparison using *50 ml of 20% sodium chloride solution to which has been added appropriate* quantities of the control solution of potassium iodide.

Modification of the Procedure

Some slight modifications of the procedure have been introduced by the Institute of Nutrition of Central America and Panama (INCAP), Guatemala, in order to improve reproducibility.

Addition of bromine. Add bromine water dropwise from a burette in a quantity equivalent to 10 mg of bromine *and let stand for 10 minutes.*

Destruction of excess bromine. Add dropwise from a burette 1% sodium sulfite solution *until only a pale yellow colour remains,* whirling the flask during the addition. Then add 2 drops of 5% phenol solution.

Liberation of iodine for titration. Add 1 ml of 2N sulfuric acid and 0 5 g *of potassium iodide and let stand in the dark for 10 minutes* Then titrate with sodium thiosulfate as indicated

Determination of Iodine in Common Salt

In preliminary survey work in goitrous areas it is necessary to ascertain the sources of dietary iodine available to the population In this connexion a knowledge of the iodine contents of the normal supplies of salt is essential.

The methods employed for the analysis of iodized salt are not always applicable to the determination of the minute amounts of iodine which

76 United States, Association of Official Agricultural Chemists (1955) *Official methods of analysis of the Association of Official Agricultural Chemists*, 8th ed, Washington, D C
77. United States Department of Agriculture (1957) *Household Food Consumption Survey 1955, Reports*, Nos 6-8
78 Van Eekelen, M. (1957) *Voeding*, 18, 336
79 Van Veen, A G (1941) *Geneesk T Ned-Ind*, 81, 2637
80 Werner, H (1930) *Z Untersuch Lebensmitt*, 60, 495
81 World Health Organization, Study-Group on Endemic Goitre (1953) *Bull Wld Hlth Org*, 9, 293
82 Wright, E & Andrews, E D (1955) *N Z J Sci Techn*, 37A, 83
83 Zinovjev, A I (1954) *Tr vsesojuz Nauk -Issledovatel Inst Solvanoi Prom*, No 1, 39
84 Zinovjev, A I (1954) *Tr vsesojuz Nauk -Issledovatel Inst Solvanoi Prom*, No 1, 66

29 Hart, E B., Griem, W. B & Clifcorn, L E. (1939) *Stabilization of iodine in salt and other feed materials*, US Pat No 2,144,150
30 Hipsley, E H (1956) *Med, J Aust*, 1, 532
31 Hirschfelder, A D (1922) *J Amer med Ass*, 79, 1426
32 Huntley, L M & Tripp, J. T (1944) *J Ass off agric Chem*, 27, 483
33 Imes, P V & Jobes, C V (1950) *Stabilized iodized salt and process of making same*, US Pat. No 2,506,568
34. Johnson, F. F & Frederick, E R (1940) *Science*, 92, 315
35 Kelly, F C (1953) *Bull Wld Hlth Org*, 9, 217
36 Khazan, V B (1948) *Gigiena*, 13, No 9, 6
37 Khazan, V B (1948) *Sovetsk Med*, 12, No 1, 30
38. Kimball, O P (1938) *Transactions of the Third International Goiter Conference*, p. 63
39 Kimball, O P. & Marine, D (1918) *Arch intern Med*, 22, 41
40 Kimball, O P, Rogoff, J M & Marine, D (1919) *J. Amer. med Ass*, 73, 1873
41 Kolomiitseva, M G (1949) *Gigiena*, No 6, 43
42 Kostl, F (1855) *Der endemische Cretinismus als Gegenstand der öffentlichen Fursorge*, Wien
43 Kruglikov, A E (1939) *Byull. Tsentral Nauch-Issledovatel Solyanoi Lab*, No 6, 29
44 McCullagh, S F (1959) *Papua N Guinea med. J*, 3, 43
45 Marine, D. & Kimball, O P (1917) *J Lab clin Med*, 3, 40
46 Marine, D & Kimball, O P (1920) *Arch intern Med*, 25, 661
47 Marine, D & Kimball, O P (1921) *J Amer. med Ass*, 77, 1068
48 Mitjašin, I A (1955) *Probl Endokr*, 1, No 1, 115
49 Mittler, S & Benham, G H (1954) *Chem Engng News*, 32, 3415
50 Murray, M M & Pochin, E. (1951) *J Physiol (London)*, 114, 6P
51 O'Dell, A E. (1952) *Manufacture of salt*, Brit Pat. No 682,709
52 Oleson, R (1927) *Publ Hlth Rep (Wash)*, 42, 1355
53 Osborn, R A, Mix, A. E & Ramsey, L L (1943) *J Ass off. agric Chem*, 26, 440
54 Paulini, E & Pereira, J P (1957) *Rev bras Malar*, 9, 515
55 Petrachkov, F A & Panchenko, L D (1958) *Vop Pitan*, 17, No. 1, 94
56 Pliška, V (1959) *Sborn Vysoke Školy Chem-techn Praze, Odd. fak potravin techn*, 3, 19 pp.
57 Pliška, V & Rykl, D (1958) *Čsl. Farm*, 7, 515
58 Preussische Bergwerks- und Hutten-A-G (1936) *Process and procedure for iodizing table and fodder salt*, German Pat No 627,061
59. Reisenauer, R & Likar, O (1958) *Čsl Hyg*, 3, 355
60. Reith, J F (1939) *Voeding*, 1, 153
61. Reith, J F (1942) *Chem. Weekbl.*, 39, 598
[illegible]

66 See, D. S. (1939) *Method of iodine fixation and product (iodised salt block) thereof*, US Pat No. 2,170,611
67. Shvets, A. S (1955) *Vop Pitan*, 14, No 2, 59
68. Smeaton, W. A (1951) *Chem Ind*, No 24, 1016
[illegible] US Pat No 1,869,518

73 [illegible]
74. [illegible]
75. [illegible]

PRINCIPLES AND PROBLEMS OF ENDEMIC GOITRE CONTROL

Dr F W. LOWENSTEIN *

There is hardly a country in the world where endemic goitre cannot be found Convincing evidence of this is presented by Kelly and Snedden in their chapter *Prevalence and geographical distribution of endemic goitre* (page 27) In many countries where endemic goitre has existed for generations, it presents a major public health problem because of its association with cretinism, deaf-mutism and mental retardation

Iodine Prophylaxis

Although the clinical picture of endemic goitre has been known for many centuries (as can be seen in paintings by Swiss and other masters of the 14th and 15th centuries), successful control measures were not developed until the present century, when modern industry provided the iodides and iodates needed for mass prophylaxis Two countries have pioneered in applying mass prophylaxis with iodine the USA and Switzerland The first controlled experiment was made in Akron, Ohio, where 5 000 schoolgirls took 0 2g of sodium iodide daily in their drinking-water for a period of 10 days in the spring and autumn [13] An equal number who drank untreated water served as controls Whereas of the girls taking the salt none of those who had a normal thyroid at the beginning developed a goitre, in the control group 50% of the girls who started out with a normal thyroid became goitrous In the girls who showed a goitre at the beginning, the thyroid regressed to normal by the end of the treatment in 66% of those taking sodium iodide but in none of the control group Following this experience, several cities in the goitre belt along the Great Lakes (e g , Rochester, N Y) started to add iodide to their central water supplies In 1924, the first successful large-scale use of iodized salt was made in Michigan with the co-operation of the salt producers, the wholesalers, and

* Medical Officer, Nutrition, WHO, Geneva, Switzerland

tion of a natural ingredient lost during the process of drying and/or refining; there are still some places—or at least have been until recently—where people are using a crude salt which has enough iodine to prevent goitre [13] In this connexion it is relevant to mention that some sea-foods—such as cod, haddock, shrimps and lobster—contain more iodine per unit of weight than iodized salt

There have been poorly-founded reports in the medical literature on cases of thyrotoxicosis (Jod-Basedow) caused by the use of iodized salt These reports have been seized on eagerly by professional and non-professional opponents of iodization to discredit this measure and discourage governments and public health authorities from supporting iodization Whereas in Switzerland and the USA this campaign failed, it did succeed in Austria, where in 1933 the government stopped the general distribution of iodized salt, started in 1924

If one looks carefully at the literature, the evidence for a toxic effect of iodized salt is, indeed, very meagre and, in the few cases published, extremely dubious Fluck [7] has presented the results of a nationwide inquiry to more than 1600 physicians in Switzerland between 1922 and 1924 A frequency of thyrotoxicosis of 5 per 100 000 was found among both the persons who consumed iodized salt and those who did not use it. Among a total of 18 cases of thyrotoxicosis supposedly due to iodized salt, only in 5 could a definite time-relationship be established between the consumption of iodized salt and the development of the toxic goitre. Wagner-Jauregg [21] showed that in quite a few of the cases diagnosed as toxic goitre due to iodized salt either the basal metabolic rate was not measured or, if it was, it was within the normal range One woman actually ate the salt in large amounts because she thought that if a little was good for her, then a bigger dose would do her even more good Among 2659 cases of hyperthyroidism, Kimball [11] saw only six which might have been related to the consumption of iodized salt, all six were in women above 40 who had had a nodular goitre of long standing In another paper,[13] he demonstrated to the goitre surgeons of the USA, who were afraid that the use of iodized salt would cause an epidemic of toxic goitre, that among 1299 adults with long-standing goitre who had been taking iodized salt for five years there was not a single case of toxic goitre which could have been diagnosed as due to the use of iodized salt The majority of the toxic patients were under treatment by a physician and had been advised, in most instances, against the use of iodized salt In recent years, Perinetti (personal communication) reported that after the introduction of iodized salt (1 30 000) in Mendoza province of Argentina he has not seen one case of thyrotoxicosis that could be attributed to the use of this salt Various authors, such as McClure [16] in Michigan and Eggenberger [6] in Switzerland, found a considerable *decrease* in thyrotoxicosis after the introduction of iodized salt Nicod stated [18] that at the time of writing (1953) no death from toxic goitre had occurred in three

the State Health Department. Within the first year, 94% of the homes were using iodized salt continuously. An excellent account of this experience has been given by Kimball in his paper on the efficiency and safety of the prevention of goitre.[12] A follow-up survey in 1936 of the four original counties showed that the goitre rate had fallen from 38.6% in 1924 to 8.2%.[a] Similar results had been obtained in Cleveland, Ohio. As a consequence, the use of iodized salt spread to other areas and became generally adopted throughout the USA.

Switzerland, the classical land of endemic goitre in Europe, took a somewhat different approach before it started using iodized salt on a large scale. Between 1923 and 1928, the goitre frequency among Swiss recruits decreased, in certain cantons, from 51.8% to 13.5% without any addition of iodine to food or water. The only thing which supposedly changed in these cantons during these five years was an improvement in the quality of the drinking-water and in the general level of hygiene.[18] Some cantons, however, introduced iodized salt as early as 1923, and by 1950, 18 cantons were using iodized salt almost exclusively. There can be no doubt that with the introduction and almost universal use of iodized salt the goitre frequency continued to decline much more rapidly among the recruits until it reached almost zero in 1945.[18] The only canton which had not accepted iodized salt up to 1950 had the highest number of goitrous recruits at that time. Simultaneously with this remarkable decrease in goitre prevalence, there occurred an almost complete disappearance of endemic cretinism. A comparative study made by the departments of pathology of the five Swiss medical schools between 1946 and 1951 has shown furthermore a marked reduction in the mean weight of the thyroid gland, a disappearance of very large goitres (weight more than 500 g), and a continuing decrease of goitre in the newborn.[20]

Objections to Iodized Salt

One of the main objections put forward to the use of iodized salt has been that iodine may have a toxic effect, particularly if used over a long period. This statement goes back to some of the early experiences in France in the 1850's when relatively high doses of iodine were used. These trials had to be abandoned because of the reported toxicity. In the dosages used for the enrichment of salt, however, the possibility of a toxic effect is very remote as they are based on the physiological requirements for iodine which have been established by careful work.[5] They depend also on the amount of salt consumed in different countries. In fact, the addition of small amounts of iodine to salt (1 : 10 000—1 : 100 000) is nothing but a restora-

[a] For further details of these trials see also the chapter *Therapy and prophylaxis of endemic goitre* on page 385 of this monograph.

country or at least all salt used in endemic goitre areas, the administrative machinery has to be created for enforcing the law At this point, difficulties often develop which delay the execution of a control programme for years. The Ministry of Health, usually charged with the execution of the programme, needs to convince the Ministry of Finance of its importance so that the necessary funds will be appropriated Even after everything has been cleared on the ministry level and production of iodized salt has actually been started, new snags may develop in the distribution Difficulties of this kind have been observed in Brazil: legislation on the iodization of all salt to be consumed in the endemic goitre areas of that country was adopted in 1954, during a nutritional survey in an endemic goitre area in the state of Minas Gerais in 1957/1958, however, it was found that practically no iodized salt was reaching the rural districts of the area Similar experiences have been reported from several other countries.

The policy to be followed by each government in relation to the enrichment of salt with iodine should depend on the extent of the local problem. In a few countries endemic goitre is confined to one or two circumscribed areas, if the local administrations are adequate for the execution of such a programme, iodization should be confined to the salt consumed in the goitre areas In most countries, however, goitre is too widespread or the local administrations are inadequately equipped for prophylaxis to be attempted on this basis, iodization must then be done centrally

An important question for any government is the cost of a preventive programme such as iodization of salt It varies, of course, from country to country, depending on the scale of the iodization process and local labour charges In the United Kingdom it is estimated to be about 5/– per ton of salt Assuming an average world price for all types of salt at £6 per ton, this means that the cost of iodizing salt amounts to less than 5% of the cost of salt At an average individual intake of 10 g per day (8 lbs per year) the increase in cost per person amounts to only 0 22d annually It is not easy to estimate the economic losses caused to a country through endemic goitre and its associated conditions, such as cretinism, etc No such estimates have been made according to our knowledge However, there can be no question that such losses in the way of ill health, possible need for surgical intervention, inability of the patient to support himself, need for institutionalization, etc, are many times higher than the actual cost of a control programme

International Collaboration in the Study of Goitre

On an international scale, interest in the goitre problem developed after the First World War The first international goitre congress took place in Bern in 1928, two other congresses have since followed, and in 1960 the

Swiss cantons since 1949 although iodized salt had been introduced in 1924, 1927, and 1946 respectively By contrast, the cantons with the lowest consumption of iodized salt (particularly Aargau, where less than 10% of the salt consumed is iodized) continued to show a higher death rate from thyrotoxicosis Clements [4] presented evidence that the steady decline in death rates from thyrotoxicosis in Australia went hand-in-hand with the decrease in the incidence of endemic goitre

It is possible that in rare instances a thyroid adenoma of long standing may become toxic in a patient taking iodized salt. The benefits from the use of iodized salt, however, to the people in an endemic goitre area far outweigh the risk of an occasional toxic effect The same philosophy applies here as in other measures of preventive medicine, such as vaccination against smallpox where the risk of encephalitis is also very remote in comparison with the beneficial protection afforded to the overwhelming majority.

Mention should be made in this connexion of the fact that some persons show a hypersensitivity to iodine in the form of so-called iodine acne and iododerma of the bullous type Dermatologists have been concerned with this problem for some time. Beerman,[2] in a recent review, has shown that there is no agreement yet among dermatologists on the importance of this question Thus, Bechet [1] reported that 38% of 240 cases of acne had been using iodized salt over long periods and improved only after discontinuing the iodized salt and taking sodium chloride instead. On the other hand, Gaul and Underwood,[9] in a three-year study of the effect of oral iodine on acne vulgaris, concluded that iodized salt does *not* have an unfavourable effect on the course of this disease. They even suggested that iodine deficiency may possibly be a contributory cause of acne. Iodine alone and its equivalent in iodized salt failed to produce pustular exacerbations. Without entering into this controversy, it is safe to assume that there may be some persons who either are hypersensitive to iodine or may become sensitized through prolonged use of small doses of iodine; for such persons non-iodized salt should be made available on a prescription basis.

Administrative Problems

If the control and prevention of endemic goitre depended on technical know-how only, the solution of this widespread problem should be at our doorstep There are, however, legal and administrative obstacles to the actual execution of such a control programme which are much more difficult to overcome. First of all, legislation has to be brought forward and adopted, before any large-scale action can be taken in any country [a] This is usually a slow process, at least in a parliamentary democracy. Then, after a law has been passed concerning the iodization of either all salt used in the

[a] See the chapter *Legislation on iodine prophylaxis* on page 453 of this monograph

Chilean Iodine Educational Bureau in London to study this problem, out of this study came a simple technique which has proved successful on a small scale and can easily be adapted to large-scale operation A second problem in this connexion is the instability of iodides in crude salt, particularly in a hot, humid climate. Again, the Chilean Iodine Educational Bureau made extensive investigations and was able to show that the answer is to use iodates instead of iodides as they are much more stable under those circumstances There was some fear that iodates would prove more toxic than iodides, but work by the Medical Research Council of Great Britain and by the Food and Drugs Administration of the US Public Health Service has shown that, given by mouth, both iodates and iodides have a very low toxicity Well-controlled field experiments in Central America by the Institute of Nutrition of Central America and Panama (INCAP) have shown the effectiveness and harmlessness of iodates [19] As a result of these activities it is now relatively easy to institute programmes of control of endemic goitre with iodized salt in almost any country in need of such a programme

Mention must also be made of the co-operation between WHO and other international organizations in this field The Joint FAO/WHO Expert Committee on Nutrition in 1954, after a review of WHO's work on this problem, recommended among other things that surveys should be carried out in various countries to determine the goitre prevalence and to provide a basis for evaluating the effectiveness of the preventive measures, particularly in regard to subsequent social and economic changes The UNICEF Executive Board, following a recommendation of the UNICEF/WHO Joint Committee on Health Policy in May 1956 that if countries put forward properly planned projects to prevent endemic goitre assistance should be given by UNICEF, agreed in principle to consider aid for such projects in October 1956 UNICEF aid was to include blending machinery for enriching salt and, in some instances, an initial supply of iodate and other materials. The countries themselves would provide the labour and materials required and undertake the necessary administrative arrangements to ensure that substantially all the salt going into the goitre-prevalent areas was enriched The first country to receive UNICEF support for goitre control was India, following the recommendations made by the UNICEF Executive Director on 11 March 1957 and 22 July 1958 With this financial help approved, the Government of India hopes to be able to produce enough iodized salt for its estimated 9-10 million people living in the goitre belt in the north of the country The Government of a neighbouring country, Pakistan, has recently requested help from WHO to provide a short-term consultant to advise on the planning, and possibly, initiate a goitre survey in that country. A similar request has been received from the Lebanon Inquiries are being received continuously by WHO from different countries regarding the technical side of salt iodization.

fourth international goitre congress is to be held in London. The World Health Organization began to interest itself in the question of endemic goitre early in its existence, and the following are the principal measures it has taken:

1. A WHO study group was convened in London in December 1952 following a recommendation of the Third World Health Assembly that WHO should make such a study and encourage governments to investigate this problem within their territories.[22] The WHO study group made some specific recommendations in regard to the technique to be used in surveys, the method of enriching salt with either iodide or iodate, and the areas for further research

2 The Third Conference on Nutrition Problems in Latin America, sponsored jointly by FAO and WHO and held in Caracas in October 1953, made more detailed recommendations on survey techniques, on levels and methods of iodization of salt, particularly under tropical conditions, and on problems for further research At the FAO/WHO Fourth Conference on Nutrition Problems in Latin America, held in Guatemala in September 1957, reports were presented on the way in which recommendations made at the third conference had been put into practice by the various countries in the regions The conference emphasized the need for implementing the legislation adopted in various countries regarding the compulsory iodization of all salt used for human consumption

3 WHO consultants have been despatched to various regions to study the problem of endemic goitre and advise governments on the measures to be taken The first consultant to undertake such a mission was Dr O. P Kimball, who had worked with Dr Marine in Ohio in the early 1920's and who had done the first surveys in connexion with the use of iodized salt Dr Kimball visited nine Latin American countries in 1950. A more extended follow-up visit, covering almost all of Latin America, was made by Dr J. Góngora and Mr J. C. M. Holman between October and December 1954 They found seven countries were already producing iodized salt, and another seven were preparing legislation concerning the use of iodized salt. In south-east Asia, the first WHO survey of endemic goitre was made by Dr Dagmar Wilson in 1950 in Ceylon. In 1955, Dr V Ramalingaswami visited Thailand to look at the nutrition situation, he reported a relatively high prevalence of goitre in the north of this country and advocated iodization of the salt used in this area. In Basutoland, Dr J. A. Muñoz, WHO nutrition officer, found that, on the average, 41% of the population suffered from endemic goitre in seven districts surveyed He advocates the use of potassium iodate for the iodization of the coarse salt used in that country.[17]

Since the iodization of the crude salt used in most developing countries presents special difficulties, WHO took the initiative and requested the

(ii) determine whether a definite relation exists between still-births or growth retardation in children and the incidence of the disease;

(iii) investigate the question whether a correlation exists between the incidence and severity of vitamin A deficiency and endemic goiter,

(iv) take advantage of dietary surveys to obtain data on the consumption of salt, foods with suspected goitrogenic activity, and other factors of possible interest in relation to the goiter problem,

(v) obtain data on the stability of iodine in salt artificially iodized with iodide or iodate under various conditions with respect to climate, storage and packaging,

(vi) study the effectiveness of prophylactic measures, by means of surveys repeated at suitable intervals, on both the incidence of goiter and the height and weight of children;

(vii) collect data on the frequency of goiter in animals

(b) Research problems

These investigations require special facilities, as follows.

(i) Additional studies to determine human iodine requirements, especially under various environmental and physiological stresses, are badly needed

(ii) Biological and chemical studies of foods with suspected goitrogenic activity are required, especially of foods habitually eaten in Latin America The presence of a goitrogenic substance as a local goiter-causing factor may possibly be demonstrated by a reduced uptake of radio-active iodine by the thyroid gland

(iii) The frequency of hyperthyroidism as well as hypothyroid activity in persons living in an endemic goiter area is uncertain and requires careful study

(iv) No adequate data are available on the relation between carcinoma of the thyroid and endemic goiter despite many indications that such a relation may exist, clinical and pathological studies of this problem should be made."

Of these projects, (i) and (ii) under *General studies* and (i), (iii) and (iv) under *Research problems* might claim priority because of their fundamental importance for the whole goitre problem As part of its intensified programme of medical research, it is the aim of WHO to stimulate experienced investigators to undertake such studies in various countries where endemic goitre is a major problem and to provide them with all possible assistance

Outstanding Problems

Putting Marine's well-known claim in the form of a question one might ask, "Is simple goitre the easiest of all known diseases to prevent?" From all available evidence the answer is, "Yes, in the great majority of known instances" However, mention should be made of the few reports where endemic goitre was found which did not respond to iodized salt, such as the one described by Clements in Tasmania.[5] The goitre in this case was *not due to a primary deficiency of iodine in the food or water, but to the* presence of goitrogenous substances in the food, particularly the milk. Obviously, the solution of such a goitre problem demands a different approach. The whole question of goitrogens in food is under intensive investigation.

There may be other goitrogens in the environment, e g, in the water McCarrison suggested in 1928 [15] that polluted drinking-water could produce goitre; he based his suggestion on epidemiological observations in the Himalayan mountains (Gilgit Fan) and on experiments on human volunteers. Hettche [10] in Hamburg continued the work on this problem and presented a hypothesis that goitrogenic activity is displayed by certain organic sulfur- and nitrogen-containing compounds (e.g, urochrome) found in polluted waters in endemic goitre areas Much more work is required to investigate the correctness of this hypothesis.

There are also indications, as found by Lowenstein in the Brazilian Amazon,[14] that an improvement in the general nutritional situation alone may go hand-in-hand with a change in the goitre picture, particularly in children Whether this change is due to an increase in iodine intake from the additional food eaten cannot be answered from the available data From such experiences it becomes clear that the problem of endemic goitre cannot be considered apart from the overall nutritional situation in a country, and, furthermore, that in the preparation of a preventive programme various factors in the environment of the people have to be considered.

The FAO/WHO Third Conference on Nutrition Problems in Latin America [8] made a number of recommendations for further work on a world-wide basis on the main questions in the public health aspects of endemic goitre still awaiting answer Since these recommendations are still as valid today as they were seven years ago, they are quoted here in their original form:

"*(a) General studies*

Public Health authorities should endeavour to:

(1) initiate investigations of the frequency of mental deficiency and deaf-mutism in areas with and without endemic goiter;

(ii) determine whether a definite relation exists between still-births or growth retardation in children and the incidence of the disease,

(iii) investigate the question whether a correlation exists between the incidence and severity of vitamin A deficiency and endemic goiter;

(iv) take advantage of dietary surveys to obtain data on the consumption of salt, foods with suspected goitrogenic activity, and other factors of possible interest in relation to the goiter problem;

(v) obtain data on the stability of iodine in salt artificially iodized with iodide or iodate under various conditions with respect to climate, storage and packaging,

(vi) study the effectiveness of prophylactic measures, by means of surveys repeated at suitable intervals, on both the incidence of goiter and the height and weight of children,

(vii) collect data on the frequency of goiter in animals

(b) Research problems

These investigations require special facilities, as follows

(i) Additional studies to determine human iodine requirements, especially under various environmental and physiological stresses, are badly needed

(ii) Biological and chemical studies of foods with suspected goitrogenic activity are required, especially of foods habitually eaten in Latin America. The presence of a goitrogenic substance as a local goiter-causing factor may possibly be demonstrated by a reduced uptake of radio-active iodine by the thyroid gland

(iii) The frequency of hyperthyroidism as well as hypothyroid activity in persons living in an endemic goiter area is uncertain and requires careful study

(iv) No adequate data are available on the relation between carcinoma of the thyroid and endemic goiter despite many indications that such a relation may exist, clinical and pathological studies of this problem should be made"

Of these projects, (i) and (ii) under *General studies* and (i), (iii) and (iv) under *Research problems* might claim priority because of their fundamental importance for the whole goitre problem As part of its intensified programme of medical research, it is the aim of WHO to stimulate experienced investigators to undertake such studies in various countries where endemic goitre is a major problem and to provide them with all possible assistance

Outstanding Problems

Putting Marine's well-known claim in the form of a question one might ask " *Is simple goitre the easiest of all known diseases to prevent?* " From all available evidence the answer is: " Yes, in the great majority of known instances " However, mention should be made of the few reports where endemic goitre was found which did not respond to iodized salt, such as the one described by Clements in Tasmania.[5] The goitre in this case was not due to a primary deficiency of iodine in the food or water, but to the presence of goitrogenous substances in the food, particularly the milk. Obviously, the solution of such a goitre problem demands a different approach The whole question of goitrogens in food is under intensive investigation.

There may be other goitrogens in the environment, e g, in the water. McCarrison suggested in 1928 [15] that polluted drinking-water could produce goitre, he based his suggestion on epidemiological observations in the Himalayan mountains (Gilgit Fan) and on experiments on human volunteers Hettche [10] in Hamburg continued the work on this problem and presented a hypothesis that goitrogenic activity is displayed by certain organic sulfur- and nitrogen-containing compounds (e g, urochrome) found in polluted waters in endemic goitre areas Much more work is required to investigate the correctness of this hypothesis

There are also indications, as found by Lowenstein in the Brazilian Amazon,[14] *that an improvement in the general nutritional situation alone* may go hand-in-hand with a change in the goitre picture, particularly in children Whether this change is due to an increase in iodine intake from the additional food eaten cannot be answered from the available data From such experiences it becomes clear that the problem of endemic goitre cannot be considered apart from the overall nutritional situation in a country, and, furthermore, that in the preparation of a preventive programme *various factors in the environment of the people have to be considered*

The FAO/WHO Third Conference on Nutrition Problems in Latin America [8] made a number of recommendations for further work on a *world-wide basis on the main questions in the public health aspects of* endemic goitre still awaiting answer. Since these recommendations are still as valid today as they were seven years ago, they are quoted here in their original form:

" *(a) General studies*

Public Health authorities should endeavour to:

(i) initiate investigations of the frequency of mental deficiency and deaf-mutism in areas with and without endemic goiter;

LEGISLATION ON IODINE PROPHYLAXIS

Dr J DE MOERLOOSE *

Introduction

Experience has shown that iodine deficiency is the essential etiological factor in endemic goitre and that iodine prophylaxis has been successful in remedying it. In Switzerland,[13, 15] for example, where iodine prophylaxis was introduced more than 30 years ago, endemic goitre has largely disappeared, and the use of iodized salt has not had any pathological consequences. At first sight it is surprising, therefore, to find that only a few countries have introduced this preventive measure and enforced it by law—or to find that this step has only been taken quite recently.

It is true that insufficient iodine intake is not the sole cause of endemic goitre. A variety of other factors, whose nature and physio-pathological mechanisms are still imperfectly understood, may play a secondary role and, in some cases, may even be of major importance.[a] Even so, the effects of these other etiological factors can usually be countered by increased iodine intake, and in most countries where goitre is endemic the reason why iodine prophylaxis has not been made compulsory by law are of quite a different nature. This emerges clearly from the study of the prevalence and geographical distribution of endemic goitre made by Kelly & Snedden, in which the measures that have been taken so far are also reviewed (see pp 27-233).

In fact, health administrations in many countries find themselves confronted with technical obstacles or policy difficulties which make it impossible to take administrative or statutory measures. While in some countries or regions the technical problem is only of secondary importance, in others it may be a very difficult one to overcome. In certain countries, only unrefined, coarsely crystalline salt is used. Furthermore, climatic factors, such as temperature and humidity, may render suitably iodized salt unstable, and thus lead to further difficulties in the way of general

* Chief, Health Legislation, WHO, Geneva, Switzerland

[a] See for example, the chapter *Etiology of endemic goitre* by J Roche & S Lissitzky, page 351

REFERENCES

1 Bechet, P E (1947) *J invest. Derm*, 8, 409
2. Beerman, H. (1949) *Amer J. med. Sci*, 218, 446
3 British Medical Association, Committee on Nutrition (1950) *Report of the Committee on Nutrition of the British Medical Association*, London
4 Clements, F W (1954) *Med J Aust*, 2, 894
5 Clements, F W & Wishart, I W (1956) *Metabolism*, 5, 623
6 Eggenberger, G (1938) *Trans. Amer. Ass Stud Goiter*, p 70
7 Fluck, W (1938) *Schweiz med Wschr*, 58, 2, 14
8 Food and Agriculture Organization of the United Nations (1954) *Report of the Third Conference on Nutrition Problems in Latin America, Caracas, Venezuela, 19-28 October 1953*, Rome, p 45 (*FAO Nutrition Meetings Report Series, No 8*)
9 Gaul & Underwood (1948) *Arch derm-syph (Paris)*, 58, 439
10 Hettche, H O (1954) *Aetiologie, Pathogenese und Prophylaxe der Struma*, Munchen, Lehmann
11 Kimball, O P (1925) *J Amer med Ass*, 85, 1709
12 Kimball, O P (1928) *J Amer med Ass*, 91, 454
13 Kimball, O P (1953) *Bull. Wld Hlth Org*, 9, 241
14 Lowenstein, F W (1959) *Amer J clin Nutr*, 7, 331
15 McCarrison, R (1928) *The aetiology and epidemiology of endemic goitre* In. *Comptes rendus de la Conférence internationale du goitre, Berne, 24-26 août 1927*, Berne, p 304
16 McClure, R D (1937) *Trans Amer Ass Stud Goiter*, p 101
17 Muñoz, J A & Anderson, M M (1959) *Bull Wld Hlth Org*, 21, 715
18 Nicod, J L (1953) *Bull. Wld Hlth Org*, 9, 259
19 Scrimshaw, N S, Cabezas, A, Castillo, F & Mendez, J (1953) *Lancet*, 2, 166
20 Uehlinger, E A (1958) *Fed Proc*, 17, Suppl No 2, p 66
21 Wagner-Jauregg (1934) *Wien klin Wschr*, 47, 321
22 World Health Organization Study-Group on Endemic Goitre (1953) *Bull Wld Hlth Org*, 9, 293

sumption was only 5% of all salt consumed This figure had risen to 30% in 1934 as a result of intensive propaganda. In 1940, the New Zealand Medical Research Council's Thyroid Research Committee recommended that non-iodized salt should be supplied only to people asking specifically for it and although this policy has not been rigidly followed, 80% of the population were using iodized salt by 1957 In the United Kingdom, the Goitre Subcommittee of the Medical Research Council noted that although individual medical men had recommended the use of iodized salt within the district that they served, there had been no public demand for it [3]

In the Netherlands,[2] on the other hand, attention was drawn to the danger of the public taking the initiative in regard to iodine prophylaxis This may lead to excessive consumption of iodine with all its attendant dangers For this reason it is essential to establish official standards

It was probably because of the above considerations that the WHO Study-Group on Endemic Goitre recommended that " all food salts should be iodized compulsorily in any country or area in which goitre is endemic, local variations in incidence of the disease being disregarded " [16]

Legislation

Most of the regulations relating to the iodization of kitchen salt and other methods of iodine prophylaxis date from 1950 onwards. However, the use of iodized salt was first made compulsory in 1924 [a] (Switzerland, Cantons of Nidwalden and Vaud) Between 1924 and 1950, similar legislation was introduced in Canada (1949), Costa Rica (1941), Hungary (1948), Mexico (1942) and the Netherlands (1942)

Apart from these legal provisions, ministerial circulars were issued in some countries (Austria, 1923; Sweden, 1936, 1950) for the sole purpose of promoting iodine prophylaxis In Switzerland also, cantonal health authorities issued circulars for the same purpose (for example, Canton of Zurich, 1923)

Nevertheless, most of the regulations of this nature have been introduced since 1950 Brazil (1953, 1956); Chile (1959), Colombia (1955) (under the terms of an earlier text of 1945 the Institute of Nutrition was created and the executive empowered to make the necessary arrangements in order to find economic ways and means of combating goitre); Bulgaria (1956, 1958), Guatemala (1954, 1955); Panama (1955); Paraguay (1954) (text establishing measures of a temporary character only); Union of South Africa (1954) and Yugoslavia (1953) It seems also that the use of iodized salt is compulsory in some parts of Northern Nigeria In the USSR, the Ministry of Health issued instructions on the iodization of kitchen salt in the period 1950-1955

[a] See also the chapter *Prevalence and distribution of endemic goitre* by Kelly & Snedden, p 27

prophylaxis based on this method. Again, some peoples may regard the introduction of refined and iodized salt with suspicion [10]

There are also questions of policy it may be difficult for the health administration of a country where there are other health problems demanding priority to persuade the legislative authorities that there is real justification for introducing iodine prophylaxis.

In addition the introduction of iodized salt raises economic problems: [13] special equipment is required, iodine compounds are expensive, and so is the labour required for homogeneous mixing and the proper packing to prevent loss of iodine Iodine prophylaxis in two countries (Argentina, province of Mendoza,[5] and Mexico,[12]) was attended by economic difficulties If, in addition to all this, it is remembered that some circles—even medical ones—are opposed to the consumption of iodized salt, it is hardly surprising that very few countries have made iodine prophylaxis compulsory However, the most simple explanation of all is that in many countries no sampling survey or systematic examination of the population has been made until quite recently. In fact, it is only as a result of such surveys that in the last few years several Latin American countries have introduced regulations making iodine prophylaxis compulsory

The various surveys have shown that endemic goitre is present, to a greater or lesser extent, in some 100 countries and territories, but of these only about ten have adopted legal measures to combat the disease In Austria, the USA[5] and the United Kingdom,[7] the recommendations of the scientific committees were in favour of the introduction of iodized salt but did not lead to the enactment of legislation

In some countries iodine prophylaxis has been applied on a purely optional basis or left to the initiative and the propaganda efforts of the health authorities This raises an important question: should iodine prophylaxis be enforced by law or should the method of persuasion and propaganda be adopted ?

The experience of various countries which have adopted one or other of these approaches shows that legal compulsion is the only rapid way to bring about the consumption of an adequate amount of iodized salt Some authors estimate that 90% of the salt consumed must be iodized if endemic goitre is to be eradicated Sollgruber [11] states that in Austria, in spite of propaganda in favour of the consumption of iodized salt, the population makes practically no use of " Vollsalz ", although they can obtain it without difficulty. In the State of Ohio in the USA, where experiments on prophylaxis with iodized salt were made even before those in Switzerland, a recent survey (1954) showed that it was still being insufficiently used.[1] In the State of Michigan,[1] there is a sharp drop in the consumption of iodized salt as soon as there is any relaxation in the efforts made to educate the public on this question. When iodized salt was introduced officially into New Zealand in 1924, its use was not made compulsory.[4] Initially, con-

Chile· 100 mg of iodine per kg of salt (1: 10 000), in the form of potassium iodide (130 mg per kg), sodium iodide (120 mg per kg), potassium iodate (170 mg per kg), or sodium iodate (160 mg per kg). If iodide is used, it must be stabilized by addition of one of the following substances or mixtures, the quantities indicated being for 1 kg of salt

(*a*) basic magnesium carbonate (10 g);

(*b*) basic magnesium carbonate (5-10 g) plus sodium thiosulfate (1 g);

(*c*) sodium thiosulfate (1 g) plus basic carbonates of magnesium and calcium (7 5 g) plus calcium oxide (1 g),

(*d*) tricalcium phosphate (10 g);

(*e*) tricalcium phosphate (9 g) plus sodium bicarbonate (0 5 g) plus dextrose (9 g).

Colombia . one part of iodine in 10 000-20 000 parts of salt

Costa Rica: one ounce of potassium iodide per ton of salt (1: 36 000)

Guatemala · addition of a mixture of potassium iodate and calcium carbonate in the proportion of 1:9, in such an amount that the final product contains not more than one part of iodine in 10 000 parts of salt nor less than one part of iodine in 15 000 parts of common salt

Hungary. 10 mg of potassium iodide per kg of salt in endemic zones (1: 100 000), 5 mg of iodide per kg of salt, against medical prescription,[14] in para-endemic zones (1: 200 000)

Mexico. 15 mg of potassium or sodium iodide per kg of salt (1· 66 000).

Panama one part of iodine in 10 000-15 000 parts of salt

Switzerland . in two cantons (Appenzell and St-Gallen), 10 mg of potassium iodide per kg of salt (1. 100 000), in the other cantons, 5 mg of potassium iodide per kg of salt (1. 200 000)

Union of South Africa not less than 10 p p m (1· 100 000) and not more than 20 p p m (1 50 000) expressed as potassium iodide (standard for "Iodine-fortified salt")

Yugoslavia 10 mg of potassium iodide per kg of salt, or an amount of sodium iodide containing the same quantity of iodine (1 100 000).

In the USSR also, ministerial instructions issued in 1950 provided for the iodization of kitchen salt in the proportion of 10 mg of potassium iodide per kg of salt

In France,[9] the Higher Health Council (Conseil supérieur d'Hygiène) recommended that the iodine content of common salt expressed as sodium iodide, should be not less than one part and not more than one-and-a-half parts in 100 000 parts No stabilizing agents should be added to iodized salt

Of the legal texts mentioned above, the only ones making the use of iodized salt *compulsory throughout the national territory* are those of Canada, Colombia, Costa Rica, Guatemala, Panama, Paraguay and Yugoslavia In Switzerland, where the authority in matters of health is decentralized, the measures are applicable throughout the cantons where they are promulgated

In Brazil, Bulgaria, Hungary, Mexico and Peru, the legislation covers only the goitrous areas In the Netherlands, the measures are applicable to certain communes. In Mexico, the law applies only to areas where more than 20% of the inhabitants are suffering from goitre, and in Brazil, only to those localities where the endemicity rate exceeds 15% in male and 25% in female children It has been suggested that iodine prophylaxis be instituted when 10% or more of children between 7 and 15 years of age show visible enlargement of the thyroid gland [6]

In Paraguay, the 1954 legislation was of a temporary character only it provided for the administration of iodized chocolate to schoolchildren for 30 weeks pending the introduction of prophylactic measures to cover the whole population

The Chilean legislation authorizes the introduction of iodized salt but does not indicate whether its use is obligatory

Obviously, the existence of a legislative text does not necessarily mean that it is applied. Stacpoole [12] refers to the fact that in Mexico (where iodized salt was to be used in the goitrous regions, in which the endemicity rate was high) the technical and economic difficulties encountered were such that, several years after the promulgation of the regulations, only a few thousand people were consuming iodized salt It is true that other techniques were used, but these were only for the benefit of schoolchildren

Levels of Iodization

1. *Iodized salt*

The most commonly used method of remedying iodine deficiency is the iodization of kitchen salt. The WHO Study-Group on Endemic Goitre [16] recommended that " food salt " be iodized in the proportion of 1.100 000 (10 mg per kg), on the basis of a daily salt consumption of 10 g It was agreed, however, that this proportion might be varied in cases where daily salt consumption has been shown to differ from 10 g The proportions of iodine or iodide required by the regulations of the various countries are as follows:

Brazil. 10 mg of iodine per kg of salt (1: 100 000)

Bulgaria: 20 g of potassium iodide stabilized with 10 kg of sodium thiosulfate and 200 g of magnesium carbonate per ton of salt (1: 50 000)

Canada: 100 mg of potassium iodide per kg of salt (1 · 10 000)

samples are taken by representatives of the health and epidemiological services of the USSR Ministry of Health or by the authorities in charge of goitre control In Colombia, the Ministry of Health is responsible for the inspection of iodized salt, it takes samples and supervises the preparation. In Guatemala, the General Association of Salt-Makers is authorized to inspect private factories preparing the salt, and is responsible for notifying the health authorities of any fault, deficiency or irregularity and for taking the measures necessary in each case to remedy such defects The Public Health Administration may also order the inspection of factories by departmental delegates or health inspectors in order to ensure that the salt is being correctly iodized. For this purpose the Administration has samples taken both where the salt is prepared and where it is distributed In Peru, supervision is entrusted to the medical officers in charge of the health units of the departments where the State salt enrichment factories are situated Such factories are required to report each month to the Department of Endemic Goitre the quantity of salt that has been iodized and to supply samples taken at both the factory and the place of distribution.

Packing and Labelling of Iodized Salt

Some regulations include conditions governing the packing and labelling of iodized salt offered for sale In Bulgaria, fine iodized salt for retail sale must be packed in containers made of parchment-paper and cardboard; salt for wholesale supply must be in a triple wrapping. The following details must appear on the packing. the name " Iodized kitchen salt ", the iodine content (mg per kg) at the time of delivery by the supplier or manufacturer, the date of production, the name of the supplier or manufacturer, and the net weight In Guatemala also, the packing must carry, in legible print, the name of the manufacturer, the manufacturer's trademark, the place of manufacture, and the countermark of the General Association of Salt-Makers In the USSR the salt is sold retail in packages of 300-1000 g and the packets, consisting of multiple wrappers, must show the following details. " Iodized kitchen salt ", quantity of iodide in mg per kg at the time of delivery by the manufacturer, the manufacturer's name, the quality of the salt, the size of the crystals, and the net weight. In Canada, the presence of iodide must be indicated on the label.

Provisions relating to Technical and Financial Assistance

The introduction of iodine prophylaxis raises technical and economic problems, but only a few of the regulations contain any provisions to facilitate the preparation and distribution of iodized salt.

In Brazil, the Ministry of Health facilitates the importation of sodium iodide or potassium iodide and supplies it at cost price to firms preparing iodized salt The National Salt Institute, in collaboration with the Health

2 *Other methods of iodine prophylaxis*

Netherlands. Formerly the quantity of potassium iodide to be incorporated in kitchen salt for use in bread-making in the communes mentioned in the relevant Ministerial Order was 31 mg per kg of salt; at the present time the quantity of iodide has been increased to 39 mg. In 1952, the use of iodized salt in bread-making was compulsory in 260 communes

Paraguay (transitional measures) Each schoolchild receives one tablet of chocolate containing 10 mg of iodine once a week for 30 weeks

Sweden (1936). The circular of 1936 states that two methods of prophylaxis are available one consists of the addition of a very small amount of iodized salt to common salt, for example 1 g of iodized salt per 10 kg, the other is school prophylaxis During the first trials, schoolchildren were given one pastille of iodized liquorice, containing 200 mg of sodium iodide, every day for ten days in spring and in autumn No cases of Basedow's disease were observed In 1950 the instructions were changed, and it is now recommended that iodized sweets should not be distributed to children except where it is certain that iodized salt is not being consumed The iodized sweets contain one mg of iodine and are distributed once a week

The regulations may provide for certain exceptions. Thus, in Switzerland, it was already possible in 1924 to obtain non-iodized salt in two cantons on presentation of a medical prescription and at the express wish of the person concerned. In Costa Rica, the salt co-operative supplies non-iodized salt to pharmacies and to persons presenting an appropriate medical certificate This prevents consumption of iodized salt by persons in whose case there is some medical contra-indication In Panama also, pharmacies may sell non-iodized salt on presentation of a medical prescription

Control of Salt Iodization

In some cases, the regulations provide for supervision of iodization factories and installations, and for analysis of samples of iodized salt to check whether the product contains the stipulated amount of iodine

In Brazil, for example, the rule is that the factories must be inspected at least every four months, and salt samples taken at each inspection In Bulgaria, iodized salt must be analysed every two months and more often if there is any suspicion of its deterioration during storage; any stock of salt whose iodine content falls below 5 mg per kg must be immediately disposed of. Requirements in the USSR (1950) are the same, the instructions also provide that consignments of salt must be accompanied by a certificate indicating the iodine content and that, if difficulties arise during transport or if the packing is defective, the salt must also be analysed on arrival. Salt

samples are taken by representatives of the health and epidemiological services of the USSR Ministry of Health or by the authorities in charge of goitre control In Colombia, the Ministry of Health is responsible for the inspection of iodized salt; it takes samples and supervises the preparation. In Guatemala, the General Association of Salt-Makers is authorized to inspect private factories preparing the salt, and is responsible for notifying the health authorities of any fault, deficiency or irregularity and for taking the measures necessary in each case to remedy such defects The Public Health Administration may also order the inspection of factories by departmental delegates or health inspectors in order to ensure that the salt is being correctly iodized For this purpose the Administration has samples taken both where the salt is prepared and where it is distributed. In Peru, supervision is entrusted to the medical officers in charge of the health units of the departments where the State salt enrichment factories are situated. Such factories are required to report each month to the Department of Endemic Goitre the quantity of salt that has been iodized and to supply samples taken at both the factory and the place of distribution

Packing and Labelling of Iodized Salt

Some regulations include conditions governing the packing and labelling of iodized salt offered for sale. In Bulgaria, fine iodized salt for retail sale must be packed in containers made of parchment-paper and cardboard, salt for wholesale supply must be in a triple wrapping. The following details must appear on the packing the name " Iodized kitchen salt ", the iodine content (mg per kg) at the time of delivery by the supplier or manufacturer, the date of production, the name of the supplier or manufacturer, and the net weight In Guatemala also, the packing must carry, in legible print, the name of the manufacturer, the manufacturer's trademark, the place of manufacture, and the countermark of the General Association of Salt-Makers. In the USSR the salt is sold retail in packages of 300-1000 g and the packets, consisting of multiple wrappers, must show the following details: " Iodized kitchen salt ", quantity of iodide in mg per kg at the time of delivery by the manufacturer, the manufacturer's name, the quality of the salt, the size of the crystals, and the net weight. In Canada, the presence of iodide must be indicated on the label

Provisions relating to Technical and Financial Assistance

The introduction of iodine prophylaxis raises technical and economic problems, but only a few of the regulations contain any provisions to facilitate the preparation and distribution of iodized salt

In Brazil, the Ministry of Health facilitates the importation of sodium iodide or potassium iodide and supplies it at cost price to firms preparing iodized salt. The National Salt Institute, in collaboration with the Health

Departments of the States concerned, gives the salt merchants technical assistance in the installation of the equipment necessary for the preparation of iodized salt. Iodized salt, in packages marked accordingly, is carried at a reduced tariff on the railways

In Guatemala, any firm producing more than 4000 quintals (400 000 kg) of salt per year must acquire and install the necessary equipment to enable it to supply iodized salt. The General Association of Salt-Makers transmits to the competent authorities the necessary applications for exemption from customs duties, etc, in order to facilitate the purchase of equipment for the preparation of iodized salt. Where the annual production of manufacturers is less than 4000 quintals of salt, the General Association of Salt-Makers must set up iodization factories for the benefit of these producers The Association provides small producers with all the facilities and technical aid necessary for the correct iodization of their salt.

REFERENCES

General

1 Brush, B E & Altland, J K. (1952) *J. clin. Endocr*, 12, 1380
2. [illegible] 4, 370
3 [illegible]
4 [illegible]
5 [illegible]
6. [illegible]
7 Murray, M M et al (1948) *Thyroid enlargement and other changes related to the mineral content of drinking water*, London (Medical Research Council Memorandum No 18)
8 Nicod, J L (1953) *Bull Wld Hlth Org.*, 9, 259
9 Quichaud, J (1956) *Sem méd prof méd.-soc.*, 32, 81
10. Ramalingaswami, V. (1953) *Bull Wld Hlth Org.*, 9, 275
11 Sollgruber, K. (1954) *Öst. Z Kinderheilk.*, 10, 312
12 Stacpoole, H H (1953) *Bull Wld Hlth Org*, 9, 283
13 Stanbury, J. B. (1953) *Chron. Wld Hlth Org*, 7, 61
14. Szabo, G & Demeczky, M. (1950) *Népegészségügy*, 31, 239
15. Wespi, H. J & Eggenberger, H U. (1957) *Bull. eidg Gesundh -Amt*, Suppl. B, p 45
16 World Health Organization, Study-Group on Endemic Goitre (1953) *Bull. Wld Hlth Org.*, 9, 293

Legislation

Brazil

Law No. 1944 of 14 August 1953, prescribing the iodization of kitchen salt intended for human consumption in the goitrous regions of the country (see *Int Dig. Hlth Leg*, 1955 *6 666*)

[illegible]

Bulgaria

Sanitary Regulations of 10 October 1956 on iodized kitchen salt (see *Int. Dig Hlth Leg.*, 1957, **8**, 608)

Extract from Decree No 18 of 3 February 1958 of the Council of Ministers, to introduce goitre control by means of iodine into areas in which goitre is endemic (see *ibid*, 1959, **10**, 599)

Order No. 367 of 24 April 1958 of the Minister of Public Health and Social Welfare, relating to the introduction of goitre control by means of iodine into areas in which goitre is endemic (see *ibid*, 1959, **10**, 599)

Canada

Office Consolidation of the Food and Drugs Act and of the Food and Drug Regulations (1954)

Chile

Decree No 387 of 13 May 1959, authorizing the manufacture and sale of iodized, purified table salt and of iodized table salt

Colombia

Decree No 0591 of 10 March 1955, instituting the preparation and use of iodized salt and fixing a period of two years within which such measures are to be carried out (see *Int Dig Hlth Leg*, 1956, **7**, 370)

Costa Rica

Decree No 6 of 24 April 1941, concerning the iodization of salt

Guatemala

Decree No 115 of 19 October 1954 (see *Int Dig Hlth Leg*, 1956, **7**, 651)

Regulations of 24 March 1955 for the application of Decree No 115 of the President of the Republic, promulgated by the Ministry of Public Health and Social Welfare, relating to the iodization of common salt (see *ibid*, 1956, **7**, 651)

Mexico

Decree of 13 March 1942, declaring the prophylaxis of endemic goitre to be in the public interest

Netherlands

Order of 23 March 1942 concerning iodized salt (see *Bull Off int Hyg publ*, 1942, **34**, 112)

Order of the Minister of 4 February 1952, determining the quantity of alkali-metal iodide to be contained in iodized salt per kilogram of kitchen salt, etc (see *Int Dig Hlth Leg*, 1954, **5**, 97)

Panama

Law No 17 of 25 January 1955, requiring the addition of iodine to common salt for consumption on the territory of the Republic (see *Int Dig. Hlth Leg*, 1958, **9**, 315)

Paraguay

Decree No 8265 of 14 October 1954, to institute control of endemic goitre in schoolchildren in Paraguay (see *Int Dig Hlth Leg*, 1958, **8**, 125)

Peru

Ministerial Decision of 9 November 1957 on the supervision of salt enrichment plants (see *Int. Dig Hlth Leg*, 1958, **9**, 811)

INDEX

The figures in bold type indicate the page numbers of chapters